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AIOC 2018

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Dr. Arup Chakrabarti

Proceedings of
76th Annual Conference of
All India Ophthalmological Society
Coimbatore, 2018

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Presidential Address

Dr. Ajit Babu Majji

Dear friends,

Our great Society has completed 75 annual conferences and now celebrating 76th. We have great history of completing 80 years from the inception. This society has got the privilege of having largest number of Native life members in the world. We have wealth of clinical data and the world's best brains. We have history of 200 years of Practice of modern Ophthalmology. We need to preserve the History, for this we need to prepare History Book of the society. A three member team, headed by Dr. Rajesh Sinha, our treasurer, will be formed to prepare history book.

Though we have world's largest number of Native life members, our annual conferences are less attended by international delegates. We need to go global, AIOS Global. All efforts shall be initiated to have more International members. At American Academy of Ophthalmology annual conferences, 25-30% of delegates are international delegates, however we have less than 5% international delegates at our annual conference. Our president elect Prof. Natarajan and Chairman Scientific Committee, Dr. Lalit Verma shall shoulder the responsibility of improving the awareness of quality of scientific content in our annual conference and work on improving international membership. All efforts shall be made in making AIOS Global a reality. To be a global leader, we shall be a big brother to the developing countries and the neighboring SAARC countries.

We shall be concentrating on Research and Publications, in view of having best of best brains and wealth of clinical data. Currently there is gross mismatch between the need and research in our country. For example, 26% of the diabetics are from India and China, however only 2% of publications are from both the countries. Our disease patterns are different from rest of the world. Our focus shall be to bringing out the disease patterns in Diabetic Retinopathy, ARMD, Myopia, Glaucoma, Optic neuritis and similar several disease entities. We need our own protocols and studies. Web Based surveys also can help in this regard. The quality of free papers presented at our annual conferences shall be improved. The conversion rate of free papers to publications is only 14.5%. These all are areas of serious concern which should be pondered upon at the earliest. We shall understand the 60% of the world's publications come from USA and Europe. Our contribution to world ophthalmic literature is only 1.7% in 2006 and slowly improving, but the rate is very low and needs drastic improvement. Majority of publications come from 9 Institutes in this vast country, there is a need for large contribution from other organizations and individual practitioner. Academic Cell to help in protocol preparation and improving Publication skills will be established and every member shall avail this facility and start publishing.

Efforts will be made to establish Knowledge Bank; Surgical wet Lab at the AIOS Head Quarters to facilitate the Members and Post – graduates to upgrade their skills. Guidelines for Competency based Post-Graduate Training Program for MS in Ophthalmology with be prepared and placed on AIOS web-site, so that all Post-Graduates can down load and follow the Standards. All the AIOS Publications will be peer reviewed here after, so as to maintain standard and the same will be circulated among neighboring countries to disseminate knowledge. The role of Chairman Academic and Research Committee, Dr. Partha Biswas and Editor Proceedings, Arup Chakrabarti is vital, in this regard.

Point system for contributions to the society will be introduced hereafter. Achievement awards will be given to maximum contributors,

so that a scientific competitive environment will be created, to encourage science in the society. Ethics and professional guidelines will be drafted and circulated to every member to follow. Disease Awareness programs shall be encouraged, by the society on its own or liaison with the government.

I would like to thank the outgoing president Dr. Santan Gopal and president-elect Prof. Natarajan and all the members of Governing Council for their support. I expect them to put in the best efforts during the year, to take AIOS to a higher pedestal. I would like to place the laudable efforts of the Members of AIOS office, for making the functioning of AIOS Headquarters appear seamless.

I request each member to contribute positively to make our society the best and to achieve the Global leadership position.

With Best Wishes

Dr. Ajit Babu Majji
President – AIOS
president@aios.org

Editorial

Dr. Arup Chakrabarti

Dear Esteemed Colleagues,

Greetings from the desk of the Editor Proceedings AIOS.

It has been my second year at the helm and it has been a pleasure to put together the best free papers of the Coimbatore AIOC conducted between February 22 and 25, 2018 in the form of the AIOS Proceedings Book - 2018. This book contains all of the 37 best papers of the sessions (BPOS) this year. 2 high quality papers were jointly declared as Col. Rangachari best paper awardees. I have also included an edited text of the AIOS president's inaugural address in this book.

In continuation of the "Go Green" drive - prevalent in AIOS - this AIOS Proceedings book will also be available to all AIOS members on the AIOS Website. However, hard copies will continue to be sent to those members who have not expressed their desire to stop receiving a hard copy as a response to the recent survey conducted by AIOS secretariat. The text of the rest of the free papers presented in AIOC 2018 are also available in the website under appropriate category headings adding great value to the post meeting resource content.

The proceedings website had been integrated with the AIOS website in 2017 and WordPress CMS had been adopted to render the content management easy. We continue to use WordPress as a platform for the AIOS proceedings website in 2018. For the first time, we have uploaded High-Resolution videos which provide more clarity for viewers.

This year an effort had been made to actively capture – in high definition - all the presentations from each of the presentation halls to the extent it was possible and upload them to the website. The contents this year too, have been formatted into invited Programmes (Symposia, Updates, Current Concepts etc), Instruction Courses, Free Papers, E-posters and Film Festival. For the convenience of the members, speaker wise videos have also been uploaded. The viewers can also

view only a particular topic of their interest. Speaker wise filters are available for easy access. Predictive search/autosuggest has been implemented. We are working on auto-generated tag cloud and related search term. I am sure the online contents are going to be far more useful and readily accessible for AIOS members than all the preceding years.

We are meticulously planning out for the next AIOS conference in Indore (2019). A new Standard Recording Procedure will be put in place very soon which hopefully will set a new benchmark for the future AV teams associated with the Proceedings team.

May I also request you to update your current address, e-mail and cell phone number with AIOS by e-mailing to aiosoffice@aios.org. I would also encourage you to pass on this information to your friends and colleagues.

I will be getting in touch with you at frequent intervals for updates.

Please don't hesitate to get in touch with me for any queries. Let all of us take AIOS to greater heights.

Yours sincerely

Dr. Arup Chakrabarti
editorproceedings@aios.org

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This Paper was judged as the **BEST PAPER** of **CATARACT I** Session.

Dr. Deepak Megur, M.B.B.S; DOMS FRCS Ed, Consultant Cataract and Glaucoma Services, Megur Eye Care Center, Bidar, Karnataka, India

Multipiece IOL In Sulcus With Optic Capture And CTR In Bag For Eyes With Weak Zonules - Does It Work?

Dr. Deepak Megur, Dr. Bharathi Megur

INTRODUCTION

Zonular weakness is a commonly encountered entity by the cataract surgeon. Trauma, pseudoexfoliation, inherited connective tissue disorders are some of the common causes for zonular weakness. Performing cataract surgery in eyes with zonular weakness is challenging for the cataract surgeon. The goals while performing surgery in such eyes is to ensure the stability of the capsular bag during cataract removal and placement of a posterior chamber intraocular lens. Capsule tension rings, segments are standard tools to stabilize the bag. Traditionally the intraocular lens is placed in the bag after the capsular bag is stabilized with Capsular tension rings. However complications associated with this technique are 1) late onset spontaneous dislocation of the capsular bag complex 2) Pseudophakodonesis 3) Capsular phimosis.

To address these issues, we propose the " IOL Trap" technique where in after placing the Capsule Tension Ring (CTR) in the bag, a multipiece hydrophobic IOL is placed intentionally in the sulcus with optic being captured in the capsulorhexis. We used this technique in eyes having subluxated cataract with localized zonular dehiscence of less than 3 clock hours, and in eyes with pseudoexfoliation with weak zonules.

AIM

To analyze outcomes of placing a multipiece hydrophobic IOL in sulcus with optic capture along with a CTR in the bag in eyes with weak zonules.

MATERIAL AND METHODS

This was a prospective non comparitive study performed at secondary eye care facility, between January 2012 to December 2016. The eyes included in the study had zonular weakness secondary to trauma or pseudoexfoliation. Eyes with traumatic subluxated cataracts with localized zonular dehiscence of less than 3 clock hours and eyes with pseudoexfoliation were include. Eyes which had gross subluxation more than 3 clock hours and also eyes with severe generalized weakness were not included in the study. A single surgeon performed all the surgeries using a standardized protocol. The surgeries were performed under posterior subtenon's anesthesia. After performing a Central Curvilinear Capsulorhexis (CCC), Phacoemulsification of the nucleus was done through a 2.8 mm clear corneal incision, followed by (in few cases preceded by) implantation of the CTR in the bag and then a multipiece hydrophobic IOL is placed in the sulcus. After removing the OVD behind the IOL the optic of the IOL is nudged posteriorly to ensure optic capture in the CCC. After removing the OVD in the anterior chamber the incisions are hydrated to ensure water tight closure. The post operative evaluation was done on the 1st day, 1 st week, 3 weeks, 6 weeks, then every 6 months for the next 4 years. Eyes with a minimum follow up of 18 months only were included in the study. The postoperative evaluation included Uncorrected & Corrected Visual Acuity, Intraocular Pressure, Dilated retinal evaluation, OCT Macula. Slitlamp photographs & HD videos with pre and post dilatation were taken to document centration of the IOL, pseudophakodonesis and capsular phimosis. The Outcome measures studied were IOL centration, capsular bag stability, pseudophakodonesis.

RESULTS

28 eyes with zonular weakness were included in the study. 20 eyes had traumatic subluxated cataracts with localized zonular dehiscence of less than 3 clock hours and the remaining 8 eyes were of pseudo exfoliation with moderate generalized zonular weakness. 15 eyes belonged to men and 13 eyes were of women. Mean age in this group was 61.17 years. 3 eyes required anterior vitrectomy to tackle the prolapsed vitreous secondary to traumatic zonular dehiscence. No other intraoperative complication noted. The mean follow up was of 23.10 months, minimum follow up was of 18 months, and the longest follow up was 38 months. Best corrected vision of 6/12 or better was achieved in 25 out of the 28 eyes. 3 eyes with BCVA of

less than 6/12 were because of epiretinal membrane in 1 eye, macular scar in 1 eye and corneal scar in 1 eye.

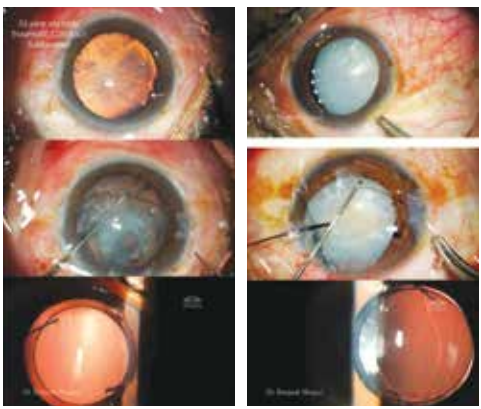
Good IOL centration was noted in 26 of the 28 eyes during the entire course of the follow up. 2 eyes had minimal IOL decentration owing to inadequate optic capture in the CCC because of a larger CCC & an eccentric CCC. 2 cases revealed mild anterior capsular phimosis at 12 months but none required any intervention during the follow up period. Mild pseudophakodonesis was noted in 16 eyes and moderate phakodonesis was noted in 6 eyes, but none of the patients found it to be bothering enough.

CONCLUSION

The IOL Trap technique consisting of placing the CTR in the capsular bag followed by intentionally placing the Multipiece Hydrophobic IOL in the sulcus with optic capture in the CCC seems to be an excellent option when dealing with eyes having subluxated cataracts with localized zonular dehiscence and eyes with pseudoexfoliation with zonular weakness. In our study period there was no evidence of late onset dislocation of the IOL bag complex, the IOLs continued to be well centered, and pseudophakodonesis was also minimal.

DISCUSSION

Traditionally in the bag IOL placement along with CTR is the norm in eyes with zonular weakness. However long term stability of the IOL Bag complex is becoming questionable as late disclocation of the IOL Bag complex is being reported. This new approach of using a CTR in the bag, followed by placing the multipiece acrylic Hydrophobic IOL haptic in sulcus with optic capture in CCC helps in better weight distribution around the IOL Bag complex. The haptics in sulcus over a period of time may get adhered to the underlying uveal tissue by fibrosis and may exert a mild anterior pull on the IOL Bag complex. Apart from this the trapping of the optic behind the CCC helps in excellent long term centration of the IOL. However it is critical to



have a perfectly sized and perfectly centered CCC to achieve good optic capture. It is also important to note that this technique is not ideal in eyes with grossly subluxated cataracts, which will do better with scleral fixation of the bag

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Clinical Outcomes Of Binocular Implantation Of Trifocal Intraocular Lens After Cataract Surgery

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ABSTRACT

PURPOSE

To evaluate visual, refractive outcomes and patient satisfaction following bilateral trifocal intraocular lens implantation after cataract surgery.

METHODS

Fifty six eyes of 28 patients that were operated in a tertiary eye care centre in Kolkata followed by implantation of trifocal intraocular lens, included in the study. A complete ophthalmic examination was performed preoperatively and postoperatively. The uncorrected and best distance-corrected monocular and binocular, near, intermediate, and distance visual acuities were measured 6 months postoperatively. In addition to the standard clinical follow-up, a questionnaire evaluating individual satisfaction and quality of life was submitted to the patients.

RESULTS

The mean age of patients at the time of surgery was 65 ± 10 years. 90% of eyes showed a spherical equivalent within ±0.50 diopters 6 months after surgery. All patients had a binocular uncorrected distance visual acuity of 0.00 LogMAR or better and a binocular uncorrected intermediate visual acuity of 0.10 LogMAR or better, 6 months after surgery. Furthermore, 80% of patients achieved a binocular uncorrected near visual acuity of 0.10 LogMAR or better. Patient satisfaction was high regarding visual quality.

CONCLUSIONS

Trifocal IOL implantation provides excellent outcomes of visual function for far, intermediate, and near distances, providing high levels of visual quality and patient satisfaction. The use of 3 foci provided significant intermediate visual results without compromising near or distance vision.

INTRODUCTION

Spectacle independence is the great challenge of modern cataract surgery. Multifocal lenses remain one of the best solution to achieve spectacle independence after cataract surgery. The optical function of the refractive multifocal IOLs derives from the refractive zones for distance and near vision allocated concentrically over the optic lens. The main disadvantage of this lens type is the significant pupil-dependence and the loss of energy in the transition zone.

Diffractive multifocal IOLs use a diffractive pattern to create an additional focus for near vision in the first diffraction order. Although part of the incident light is intrinsically lost at higher orders of

diffraction, studies have shown that the IOL offers good distance and near visual acuity (VA).[1]

Diffractive IOLs achieve better optical quality, based on optical bench measurements, than refractive multifocal IOLs.[2-3] Publications presenting results from clinical studies indicate better contrast sensitivity after diffractive IOL implantation than for refractive multifocal IOL implantation for equivalent visual acuities.[3]

However, most studies also report poor scores for intermediate vision, correlating to worse intermediate visual acuity.[4-5] It has also been reported that the implantation of bifocal diffractive IOLs leads to a higher percentage of spectacle dependent patients, especially for intermediate distance vision.[5]

Hence, the quality of vision with multifocal IOLs is a real concern. In many cases, photic phenomena (glare, halos, positive or negative dysphotopsia) are described after multifocal lens implantation which result in blurred vision.[6] Multifocal IOLs do not cover the full range of vision and often have insufficient intermediate vision.[7-9]

Our purpose of the study was to evaluate visual, refractive outcomes and patient satisfaction following bilateral trifocal intraocular lens implantation after cataract surgery.

METHODS

This retrospective study comprises 56 eyes in 28 consecutive patients who had cataract surgery followed by bilateral implantation of the trifocal IOL between April 2016 and March 2017 at a tertiary eye hospital in Kolkata. The guidelines of the Helsinki Declarations were followed, and informed consent was obtained from all patients.

Trifocal intraocular lens combines two diffractive patterns, one adding +3.50 diopters (D) for the near vision and the other one +1.75 D for the intermediate vision. An asymmetric distribution of energy among the three foci (near, intermediate, and far) allows for dominant distance vision, improved intermediate vision, and no impacted near vision. The IOL is based on a fully diffractive optic with gradual attenuation of the diffractive step height throughout the entire optic, resulting in a continuous change of the light energy distribution directed to the three primary foci. The percentage of lost energy for typical bifocal diffractive IOLs is 18%–20%, while it is approximately 15% for the trifocal IOL. This is due to accumulation of the energy from the second order of the diffractive pattern for the intermediate vision

(+1.75 D) to the energy from the first order of the diffractive pattern for the near vision (+3.50 D).[10]

Detailed preoperative examination was done. VA was measured using a Snellen chart, intraocular pressure using a Goldmann tonometer, axial length and keratometric values using the IOLMaster 500 (Carl Zeiss Meditec, Jena, Germany). A slit lamp examination of the anterior segment and an indirect ophthalmoscopy were performed. Exclusion criteria was diabetic retinopathy, age-related macular degeneration, cornea guttata, or pseudoexfoliative syndrome, corneal astigmatisms greater than 1.75 D. The patient's expectations regarding spectacle independence and visual quality were also assessed and explained.

One surgeon performed the surgeries using a standard bimanual phaco-chop technique of sutureless micro incision, phacoemulsification, and topical anesthesia. Postoperative topical therapy included a combination of topical antibiotic and steroidal agents.

The patients were examined at first postoperative day, then 1 week, 1 month, 3 months and 6 months after surgery. In every visit, details anterior and posterior segment evaluation done along with intraocular pressure. Uncorrected and corrected visual acuity was measured at near 33 cm, Intermediate at 67 cm, 100 cm and distance using snellen visual acuity chart, then converted to LogMar chart. All measurements were done in same room both preoperatively and postoperatively – usually at both mesopic and photophic condition.

The contrast sensitivity test was performed under same room light preoperatively and postoperatively using Pelli Robson Contrast Sensitivity Chart. The patients were surveyed using a quality of life questionnaire.

The results are presented as the mean ± standard deviation (SD) and were calculated using Excel worksheet 2007 software and statistically analyzed using SPSS Version 22. Differences were considered statistically significant when the P value was less than 0.05.

RESULTS

The mean age of patients at the time of surgery was 65 ± 10 years. 90% of eyes showed a spherical equivalent within ±0.50 diopters 6 months after surgery. Mean binocular uncorrected distance visual acuity of LogMAR 0.05 ± 05 or better and a binocular uncorrected intermediate visual acuity of LogMAR 0.1 ± 0.05 or better, 6 months after surgery. Furthermore, 80% of patients achieved a binocular uncorrected near visual acuity of LogMAR 0.1±0.05 (Fig- 1)

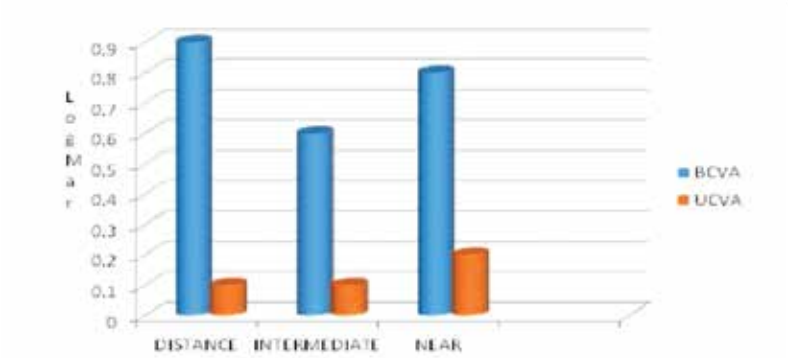

Fig.1: Best Corrected Visual Acuity and Uncorrected Visual Acuity

Mean Log Mar contrast sensitivity was improved uptoLogCS 1.95 (Range 1.35 – 2.25). (Fig – 2). Patient satisfaction was high regarding visual quality.

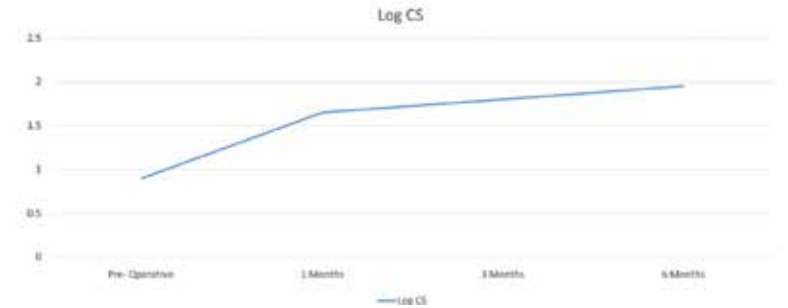

Fig. 2: Preoperative and Postoperative Contrast sensitivity in LogMar Scale

A summary of the questionnaire answers regarding the photic phenomena is given in Figure 3. 18% percent of the patients reported spontaneously seeing halos, 8% on inquiry, but halos were not seen by 74% of the patients. Nevertheless, the halos were not considered to be bothersome.

Fig.3: Status of patient satisfaction with trifocal implantation after cataract surgery

The quality of vision was then assessed with respect to the preoperative condition. The quality of vision was estimated to be good for watching TV and book reading

in 100% of cases and was good for needle work in 85% of cases. Spectacle independence was achieved for 90% of eyes for distance vision and for 85% for near vision. In the 15% of the patients requiring spectacles for near vision, half of them only needed their spectacles for very small characters.

DISCUSSION

The optical principles of the multifocal IOL are very different from the trifocal IOL; the former being made of concentric diffractive zones allocated to near, intermediate, and distance visions, combining diffractive and refractive IOL principles.[3] The purpose of this study was to analyze the objective and subjective outcomes after the implantation of a diffractive trifocal IOL, and to compare the clinical findings with the theoretical findings in previous literatures.

The outcomes with the trifocal IOL are good for intermediate and near vision, and are similar to the outcomes of several studies on the implantation of multifocal IOLs that have been reported in a recent article from de Vries et al.[8] Furthermore, the distance and near visual acuities are maintained with the trifocal IOL while enhancing the intermediate visual acuity.

Optimum VA outcomes are confirmed by the percentage of spectacle independence, which is comparable with any of those reported in other studies.[11] Spectacle independence is achieved for 90% of eyes for distance vision and for 85% for near vision with the trifocal IOL. In the 15% of the patients requiring spectacles for near vision, half this number need them for very small characters only.

Multiple studies show compromised contrast sensitivity in multifocal IOL implantation. This also increase glare and halos in dim light condition.[12] Our study shows mean log contrast sensitivity is LogCS 1.95 with minimum glare and halos. Patients also shows high level of satisfaction in their questionnaire.

The study by de Vries[13] et al showed that 38.2% of patients were dissatisfied after implantation of a multifocal IOL because they experienced major photic phenomena, with or without blurred vision. There is an important discrepancy between the reported rates of subjective photic phenomena.[14] This discrepancy could be due to the explanations given to the patient by the surgeon to describe photic phenomena. Glare can be translated as sensitivity to light (dazzle) or as the sensation of a white veil in front of the actual image. Halos

can also be explained in two ways: dazzle with light or rings around lights.

The trifocality does not appear to introduce any additional problems to those reported for diffractive bifocal MIOLs. This may be explained by the number of diffractive steps (26 steps) used in the FineVision IOL, which is lower than that for other diffractive IOLs (32 for the Tecnis and 28 for the Acrilisa), thus reducing the halos induced by the diffractive edges.[13] In addition, FineVision shows convoluted diffractive steps, ie, with smoothed edges. Halos are therefore attenuated compared to more or less convoluted IOLs with sharp diffractive steps.

CONCLUSION

Trifocal IOL implantation provides excellent outcomes of visual function for far, intermediate, and near distances, providing high levels of visual quality and patient satisfaction. The use of 3 foci provided significant intermediate visual results without compromising near or distance vision and thus good spectacle independence. The trifocal diffractive IOL induces minimal photic phenomena (halos, glare). The contrast sensitivity did not decrease as other multifocal IOL and provides excellent patient satisfaction.

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One-Year Clinical Outcomes With A New Design Of Posterior Chamber Capsular Fixation Intraocular Lens

Dr. Sheetal Brar, Dr. Sri Ganesh

ABSTRACT

Purpose: To report the feasibility of implantation and one year mean outcomes of a new design of anterior capsule fixated intraocular lens (IOL)

METHODS

The new IOL design is a foldable, hydrophilic, open loop PCIOL with two extra PMMA swivel haptics created on the optic surface to capture the anterior capsulotomy after the IOL is implanted in the bag.

RESULTS

The new IOL was implanted in 25 eyes of 25 patients with mean age of 65 years, of which 19 eyes underwent phacoemulsification and 6 eyes had laser cataract surgery. Post-operatively, from 1 week through an average of 12 months (range 5-18 months) all eyes showed stable refraction and anterior chamber depth with no evidence of decentration or tilt. All eyes had a post-operative residual spherical equivalent (SE) within ±1.5 D. Subjective questionnaire revealed high patient satisfaction with no complaints of dysphotopsia. Two eyes had minimum evidence of PCO at 8 months. No eye required explantation of IOL by the end of mean follow-up.

CONCLUSION

The new IOL design was feasible to implant and provided satisfactory outcomes in terms of no dysphotopsias or any adverse incidents. However, the long term effects on stabilisation of effective lens position due to capsular contraction, and PCO need to be verified, until all study eyes achieve a minimum post-operative follow-up of 12 months.

KEY WORDS

Posterior chamber intraocular lens swivel haptics capsule fixation, effective lens position, dysphotopsia

INTRODUCTION

Modern day cataract surgery has become a refractive surgery as patients desire spectacle free vision post operatively. Most of the variables influencing post-operative refraction have been overcome by advancement in keratometery, optical biometery and newer generation intraocular lens(IOL) calculation formulae.[1,2] However, refractive surprises, IOL tilt, rotation, decentration, PCO, dysphotopsia continue to be the causes of patient dissatisfaction after a perfect cataract surgery.[3]

To overcome these problems, various capsule fixation lenses have been investigated.[4,5,6] However, some of these IOL designs may be

associated with intra and postoperative complications such as capsulotomy tears, capsular block, iris chaffing and pigment dispersion. Other potential limitations could be difficult and incomplete removal of ocular viscoelastic device (OVD) from the bag behind the IOL, complicated designs and need for special injectors.

Concept of a new design of capsule fixation IOL

The new IOL design is a single piece, open loop, hydrophilic acrylic IOL with 6 mm aspheric optic, bearing a 360° square edge and an overall diameter of 13 mm. The lens has 2 extra haptics on the optic at 3 and 9 o'clock positions made of PMMA, which can swivel over a pivot. The technical specifications of the IOL design have been provided in Table 1.

Table 1. Specifications of the new "Swivel hapticscapsulotomyfixated IOL"

Optics Characteristics	
Powers	+18 D to +24 D
Diameter	6 mm
Shape	Aspheric
Material	UV-blocking hydrophilic acrylic
Refractive Index	1.462 at 35°C
Edge design	360 degrees square edge
Haptics Characteristics	
Overall length	13 mm
Fixed haptics	
Design	Open/C-loop
Material	Hydrophilic acrylic
Number	2 in number
Movable (Swivel) haptics	
Design	Straight
Material	PMMA
Number	2 in number
Length	2 mm
Optical A-Constant	117.5

Preoperative considerations and biometry: The IOL power is calculated using the IOL Master 700 (Carl Zeiss Meditec, Germany) using the SRK/T formula. The recommended A-constant used for the new lens is 117.5, considering a relatively anterior position of the IOL compared to in the bag IOLs, where generally the A-constant used is between 118.2 to 118.7.

The new IOL design is suitable for implantation following a routine phacoemulsification or a femtolaser assisted cataract surgery. The most important prerequisite for implantation of this lens is an intact, circular and continuous curvilinear capsulorhexis (CCC) between 5.0-5.5 mm size. Relative contraindications for implantation of this lens are too small or too large capsulotomy, uneven or eccentric capsulotomy, torn capsulotomy, moderate to severe pseudoexfoliation (PXF) and intra-operative posterior capsule rupture or zonular dehiscence associated with vitreous loss.

Loading and implantation of the IOL (video clip1): The IOL can be implanted using a regular pusher type injector through a 2.8 mm incision. While loading, both the swivel haptics are rotated and folded on to the optic using a Sinskey's hook while aligning them parallel to the longitudinal axis of the IOL. The IOL is then loaded in the cartridge while maintaining this alignment and then injected into the eye through a standard 2.8 mm incision. First, the optic with all the 4 haptics are positioned in the bag. After this, two Sinskey's hooks are introduced one from the main port and another from a side port to maneuver the IOL. The side port hook is used to gently push the optic towards the center and stabilize it, while the main port hook is used to rotate the swivel haptic and capture it on to the capsulotomy. In a similar manner, the second swivel haptic is also fixated to the capsulotomy on the other side. Viscoelastic is then aspirated from anterior chamber and the bag by gently tapping on the surface of the IOL. Folds in the posterior capsule at the end of surgery, indicate that most of the viscoelastic has been removed from the bag. Stability of the IOL is checked on table. Upon completion of surgery, wound is hydrated and sealed.

25 eyes of 25 patients (mean age 65 years), were implanted with the new lens and followed up for an average of 12 months (range 5-18 months). All eyes had a least follow- up of 5 months. 19 eyes had phacoemulsification, while 6 eyes had femto assisted laser surgery. The study was approved by the institutional ethics committee of our hospital and informed consent was obtained by all patients participating in the study.

RESULTS

Initial experience suggested that the IOL was feasible and safe to implant without any intraoperative complications of capsulotomy tears or haptic breakage while capturing the swivel haptic on to the capsulotomy. None of the lenses were explanted.

Figure 1. shows results of post-op SE predictability: 7 eyes had post op SE within ±0.5 D, while all eyes had post-op SE within ±1.5 D at the end of mean follow-up period.

Fig. 1: Post-operative SE predictability at the end of mean follow-up

Postoperatively, dilated clinical photography showed stable position of the lens and swivel haptics with no evidence of decentration, tilt or rotation. Figure 2 shows the clinical photographs of an eye implanted with the new IOL following routine phacoemulsification at 2 week and 6 months follow up.

Note the stable position of the swivel haptics without any tilt or decentration over time. Anterior chamber depth (ACD) measured with IOL Master 700 also showed no significant change at 12 months mean follow-up (4.26 mm) compared with two week follow up (4.24 mm) (p value =0.08).

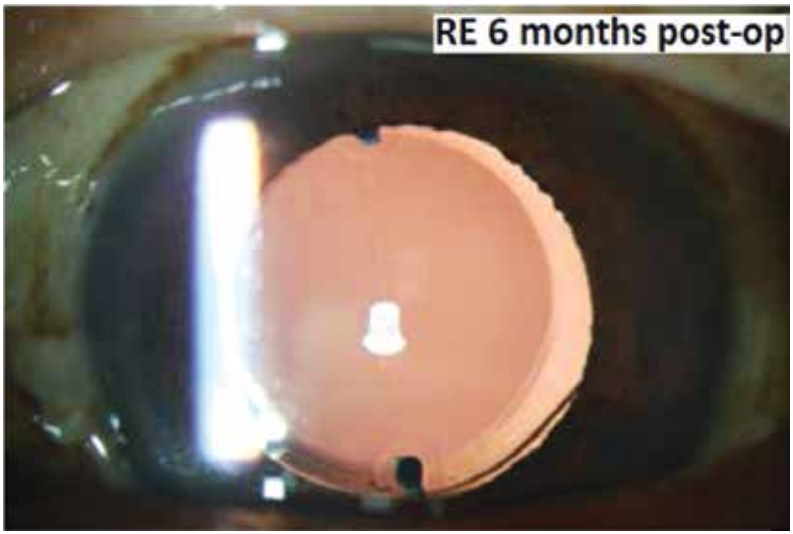

Fig. 2: Clinical photograph of an eye at 2 weeks and 6 months after implantation of the swivel-haptics capsule fixation IOL showing a stable position of IOL, without any rotation, tilt or decentration

Ultrasound Biomicroscopy (UBM) demonstrated the effective lens position (ELP) to be more anterior and just behind the iris plane as compared to conventional in the bag lenses, where it is expected to be more posterior (Figure 3).

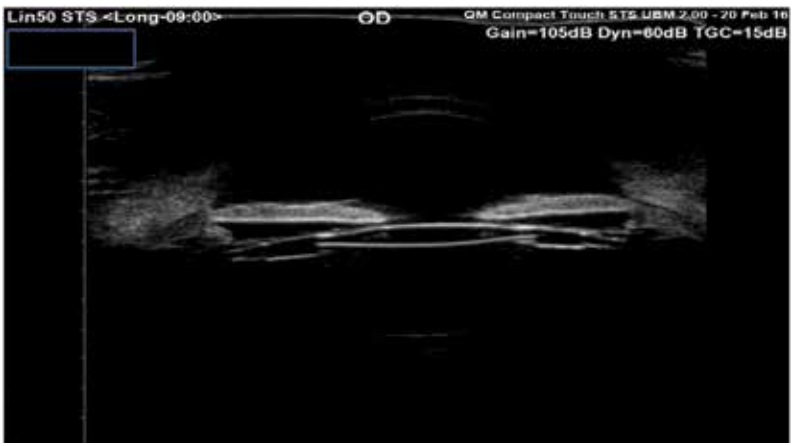

Fig. 3: Ultrasound Biomicroscopy (UBM) of an eye at 2 weeks post implantation of the swivel-haptics capsule fixation IOL showing the effective lens position of the IOL to be just behind the iris and much anterior compared to conventional in the bag implantation

No evidence of iris chaffing, pigment dispersion, secondary glaucoma or capsular block syndrome was observed in any of the eyes implanted with the new IOL at the end of the mean follow-up. Two eyes had evidence of mild visually nonsignificant PCO beginning at 8 months, which did not require YAG capsulotomy.

DISCUSSION

The new swivel haptics anterior capsule fixated IOL design potentially overcomes most of the limitations of the previously introduced capsulotomy fixation IOLs. Bag- in- the- lens (BIL, Morcher GmbH, Stuttgart, Germany) was the first capsulotomy fixated IOL introduced in 2006, mainly for the purpose of obviating the need of Yag laser capsulotomy.[4] The long term outcomes in adult and pediatric eyes showed the IOL to be safe for implantation and effective for reducing the incidence of PCO. However, the surgical technique involved placement of the anterior and posterior capsules in the IOL's groove after a capsulorhexis of the same size created in both capsules using a special anterior capsulorhexis ring caliper.[7] Therefore, this surgical technique appears to be more challenging, thus requiring a higher degree of surgical skill.

The 90 F intraocular lens (Morcher GmbH, Stuttgart, Germany) has the design of a C-loop intraocular lens with an additional flank. In contrast to the femtosecond laser-assisted in-the-bag lens technique, only the anterior capsule is fixated in the side flank, whereas the posterior capsule is kept intact and the IOL is implanted in the capsular bag.[5] However, the risk of tearing of capsulotomy or capsular block syndrome still needs to be evaluated with this lens. The new swivel haptics anterior fixated IOL, by virtue of its simple design and lesser manipulation of the capsulotomy may be potentially associated with lesser risk of capsulotomy tears. Also, observation of folds in the posterior capsule at the end of surgery suggested, almost a complete removal of the OVD, minimizing the chances of capsular block syndrome due to OVD retention in the post-operative period.

Preussner et al emphasized that knowledge of post-operative ACD is important to accurately predict the postoperative IOL position and refraction.[8] This, however, cannot be easily predicted as the capsular bag size differs in individuals and there is a variable degree of capsular contraction over time. Following the new IOL implantation, however, the IOL position is shown to be just behind the iris (on UBM) due to capsule fixation, negating the influence of bag size on the effective lens position (ELP) to a great extent. This may help

better prediction of postoperative ACD, based upon which the A-constant can be refined for improving predictability of post-operative refraction. Thus, a stable fixation and ELP may be achieved which may not be influenced by capsular changes over time. However, this aspect needs to be verified over a longer follow-up period i.e. all eyes completing at least 12 months follow-up.

According to one of the theories, negative dysphotopsias (ND) were more likely to develop in postoperative eyes in which there was a larger distance between the back of the iris and the anterior capsule of the lens.[9] Since the new IOL is captured on to the anterior surface of the capsulotomy, it brings the IOL position more anterior compared to in the bag lenses, thus reducing the distance between back of the iris and anterior lens capsule, consequently preventing negative dysphotopsias. However, the Masket TM ND IOL negates dysphotopsia through a different mechanism by allowing for the implant to be capsule bag fixated and provides a flange of the anterior optic edge to override the anterior capsulotomy.[6]

Regarding the occurrence of PCO, it may be proposed that the incidence of PCO with new swivel haptic IOL may be similar to the conventional in the bag IOLs. This may be due to the uniform shrink wrap effect and the 360° square edge of the IOL optic preventing the lens epithelial cells (LECs) to migrate and proliferate towards the optical center.[10] Two eyes showed minimum PCO at 8 months, which was not significant and did not require YAG capsulotomy. Since all eyes did not reach 12 months follow-up and the minimum follow-up was 5 months, the long term outcomes in terms of PCO development still need to be seen until all eyes complete 12 months follow-up.

Other potential advantages are simple design, easy to manufacture and pack, can be used with standard injector through 2.8 mm incision and needs no special instruments or surgical training. Also, the swivel haptic fixation ensures rotational stability which may provide significant advantage for toric designs, irrespective of bag size. Lastly, the IOL is easy to explant by simple disengagement of the swivel haptics, if required.

In conclusion, our initial experience with the new IOL with swivel haptic capsule fixation suggests that it may be a safe and feasible alternative to the conventional PCIOL designs potentially providing a stable IOL position and low incidence of dysphotopsia, and without

any visually threatening intra or post-operative complications. However, prospective clinical trials with a larger number of patients are necessary to confirm these early findings, investigate long term results in terms of effective lens position stabilization and PCO and to optimize A- constants.

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This Paper was conferred with the **AIOS-SANTE VISION AWARD** for the **BEST PAPER** of **ALL CATARACT** Sessions. This paper was also judged as the **BEST PAPER** of **CATARACT IV** Session.

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Punchorhexis

Dr. Mohan Rajan, Dr. Sujatha Mohan

INTRODUCTION

The most challenging step in handling an intumescent cataract is the creation of a well-sized round and centered Continuous Curvilinear Capsulorhexis (CCC). In these mature cataracts, the capsule tends to be thin and fragile and the absent red reflex results in poor visualization of the capsule edge during capsulorhexis.[1,2] Due to the high intralenticular pressure.[3,4] the capsulorhexis tear has a tendency to extend to the periphery, forming a radial tear that produces the Argentinian flag sign. This may progress to complications including zonular or posterior capsule tears, vitreous loss, and intraocular lens (IOL) decentration. Recently, new methods such as the femtosecond laser capsulotomy, the nanopulse capsulotomy (Zepto, Mynosys Cellular Devices, Inc.), and Capsulasor (Excel-Lens, Inc.) in which the laser is selectively absorbed by the trypan blue staining the capsule, have been introduced. Although these technologies automate the capsulotomy and reduce the dependence on surgical skill, they add to the cost of the cataract procedure. Furthermore, whether these technologies safely create a complete capsulotomy in intumescent cataracts has not been studied.

In this study, punchorhexis a novel method is attempted where simultaneous puncture of the anterior capsule and decompression of the capsular bag done there by causing decrease in intralenticular pressure. It is therefore crucial in preventing an uncontrolled radial extension of tear (Argentinian flag sign).[5,6]

PURPOSE

To prevent Argentinian flag sign during capsulorrhexis in white mature and intumuscent cataracts.

MATERIALS AND METHODS

It is a prospective interventional study done over a period of 6 months. 242 eyes with white intumescent cataract were included in this study. All patients underwent detailed ophthalmological examination which included Slitlamp examination, A scan, B scan, preoperative IOL power calculation (IOL Master Carl Zeiss) and Intraocular pressure measured by non contact tonometry.

Exclusion criteria were history of coexisting ocular diseases like uncontrolled glaucoma, ocular tumors, ocular trauma, pseudoexfoliation syndrome, zonular dialysis, poorly dilating pupil (pupil <6 mm).

SURGICAL TECHNIQUE

The same experienced surgeon performed all phacoemulsification procedures using the same technique. Under Peribulbar anesthesia, the volume of anesthetic injected should be adequate to induce akinesia and analgesia but not a firm globe. Globe compression should be performed if the eye is firm after the injection. The side-port incision is made, and then the main temporal clear corneal incision is created using a keratome. The capsule is stained with 0.06% trypan blue and the anterior chamber completely filled with OVD. Using the main corneal incision, phacoemulsification probe inserted into anterior chamber and Punch capsulorhexis was done with a bevel down 15 degree phaco needle using high vacuum and burst phaco (Vacuum : 350 - 400 mmHg, Phaco Power : 40%). Due to sudden burst of phaco power there is sudden decompression of lens bag and decrease in intralenticular pressure. Once the punch was made the capsulorrhexis was completed with Utrata forceps. Phacoemulsification was further performed without hydrodissection using a Stellaris phacoemulsification system followed by foldable hydrophilic single piece acrylic IOL implantation.

RESULTS

The study comprised 242 eyes of 242 patients. The mean age was 65.3 years. The punchorhexis prevented Argentinian flag sign in 239 (98.7%) eyes out of 242 eyes. Postoperatively there were no complications

DISCUSSION

An intumescent lens puts the surgeon at risk for Argentinian Flag Sign during capsulorhexis, running away of rhexis, posterior capsular tear, zonular rupture. Simultaneous puncture of the anterior capsule

and decompression of the bag is therefore crucial in preventing an uncontrolled radial extension of tear.[7,8] This technique not only ensures the initial decompression, but also prevents a catastrophic Argentinian flag sign. It also facilitates the controlled creation of a capsulorhexis of a desired size. However, in eyes with phacomorphic glaucoma in which the anterior chamber is extremely shallow, this technique may be challenging, especially when the cornea becomes hazy with an increase in intraocular pressure during the CCC procedure.

In conclusion, Punchorhexis technique for intumescent cataracts is a successful and reproducible method of achieving a well-sized CCC.

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Smart Way Of Diabetic Retinopathy (DR) Screening – A Comparative Study

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INTRODUCTION

Diabetic eye disease (DED) secondary to diabetes mellitus (DM) is the most common cause for blindness during working age worldwide.[1] However, due to lack of medical care the disease is under-diagnosed in developing countries. Up to two thirds of diabetic patients are undiagnosed.[2] In rural areas of South India the prevalence is up to 10%.[2,3] Out of these, 18 – 34% has diabetic eye disease (DED) on initial diabetes diagnosis.[4-9] 74% of India's population live in rural areas with limited access to medical care.[10] DED will affect almost every diabetes patient within 15 years following diagnosis.[11] Blindness caused by diabetes, however, can be prevented in nearly all cases by an early diagnosis, optimization of risk factors and early management of ocular complications.[1, 7,12] Access to health care and lack of sophisticated instruments makes diabetic retinopathy screening a challenge in remote areas. Using smartphone based as a direct ophthalmoscope for diabetic screening in such remote areas would make eye care accessible and hence preventing blindness related to diabetes. Many smartphone based fundoscopy devises are available in the market. They are PEEK retina, D Eye, Paxos and DIY. So far there is no comparative study between these devices.

AIM

In this study we compare efficacy of two smartphone based direct ophthalmoscope devices [D EYE and do it yourself solution (DIY)] with a non mydriatic fundus camera (3 netra)

MATERIAL AND METHODS

This is prospective cross sectional study conducted at a tertiary eye

care hospital. In this study 200 patients with diabetes were screened in different outreach camps at both rural and urban areas. Aim of this study was to compare two different smartphone based direct ophthalmoscope devices (D Eye and DIY) for diabetic retinopathy screening in South India.

We included diabetic patients who attend screening camp. We excluded patients with shallow anterior segment, severe media opacities and patients who are allergic to dilating eye drops. Screening camps were conducted at both rural and urban areas.

After dilatation with 5% phenylephrine and 0.8% tropicamide fundus was examined with D Eye, DIY and 3 netra. Videos from smartphone based devices were acquired from the optic nerve head, the macula and the four arcades and 7 field photos was taken with 3 netra. For the smartphone-based examination the following acquisition protocol will be applied: optic nerve head (ONH), lower temporal arcade centrifugally, macula, upper temporal arcade from periphery to ONH, lower nasal arcade centrifugally, upper nasal arcade from periphery to ONH. DED will be graded according to the International Clinical Diabetic Retinopathy Disease and Macular Edema Disease Severity Scale proposed by the Global Diabetic Retinopathy Project Group. The screening of patients was done by trained optometrists and doctors. The images acquired by each device were assessed for presence of diabetic retinopathy, field of view, image quality consisting of sharpness, reflexes, illumination. Grading scale was devised for each parameter is described in Table 1. The images were assessed for sensitivity and specificity for ability to identify diabetic retinopathy and diabetic maculopathy and to assess the need for referral. Field of view was assessed using ImageJ software. The images were assessed by two qualified observers. Inter observer variability was also calculated. 3 netra was considered as the gold standard device and images from D Eye and DIY were compared to the images from 3 netra.

Informed consent was obtained from all the participants and institutional

Table 1: Grading scale for parameters assessed

Sharpness	Reflex artifacts	Illumination
Visible in at least 75% of the video: 0 = no vessels visible at all 1 = only first order vessels 2 = only second order vessels 3 = only third order vessels	Present at least 75% of the video and blocking X% of the field of view: 0 = >50% 1 = >30% 2 = >10% 3 = <10%	At least 75% of the video: 1 = bad illumination 2 = medium illumination 3 = good illumination

ethical and scientific committee approval was obtained prior to commencement of the study.

RESULTS

Two hundred patients were included in the study. Of the 200 patients 40 patients had diabetic retinopathy. Of the 40% (n= 16) of cases with diabetic retinopathy needed referral to higher center for further treatment.

Reflex artifact seen in D Eye-grade 0 in 39% and grade 1 in 59%, whereas in DIY it was grade 0 in 16%, grade 1 in 16%, grade 2 in 41% and grade 3 in 25% of the eyes.

Illumination in D-Eye was grade 1 in 61.5%, grade 2 in 38.5%, whereas in DIY it was 58% in grade 1 and 42% in grade 2 ($p>0.05$).

Sharpness of image in D-Eye was grade1 in 7.6%, grade 2 in 76.92% and grade 3 in 15.38%, in DIY grade 1 in 7.6%, grade 2 in 53.84% and grade 3 in 30.7%.

There was good agreement between grading done by the two observers.

DISCUSSION

Screening of diabetic patients is a very effective tool in preventing vision threatening complications. Mobile phone being ubiquitous can be a cost effective and a portable alternative to conventional fundus camera.

Out of 200 patients, diabetic retinopathy was detected in 40 patients, this correlates well with the known prevalence of diabetic retinopathy (20%) in patients with diabetes. Diabetes being a posterior pole disease can be easily identified by direct ophthalmoscope.

In this study we found that sharpness of the image was better with DIY when compared to D-Eye. Illumination of the fundus with DIY was better when compared to D-Eye. The field of view was greater in DIY when compared to D-Eye.

Both smartphone based devices could identify diabetic retinopathy with same sensitivity as that of the gold standard device (3 Netra). This proves that the two smartphone based devices were effective in identifying the presence of diabetic retinopathy.

Reflexes seen while acquiring the video hampered the quality of image and hence hampered image grading in few cases more so in D-Eye when compared to DIY. These reflexes can be avoided to some extent by tilting the smartphone.

DIY from having better sharpness, illumination and field of view when compared to D-Eye. DIY is easy to assemble with an added advantage of being cost effective. DIY is approximately 150 times cheaper when compared to D-Eye. (The estimated cost of D-Eye is Rs 30000 and DIY is Rs 200)

Limitation of these smartphone devices are limited field of view, inability to image eyes with media opacity. Limitations of this study are small sample size and considering 3 netra as gold standard instead of clinical examination.

To our knowledge ours is the first study which compares these two smartphone based direct ophthalmoscopes. Smartphone based devices can be a cost effective and a feasible screening tool for diabetic retinopathy.

CONCLUSION

Smartphone based direct ophthalmoscope devices are effective in screen patients with diabetic retinopathy. Both D eye and DIY were found to be effective in detection of diabetic retinopathy. DIY had better feel of view and less artifacts due to reflexes when compared to D eye. D eye had better illumination when compared to DIY.

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Visually Disabling Neuro Ophthalmological Diseases In Professional Drivers

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ABSTRACT

AIM

To assess neuro ophthalmological diseases in professional drivers which can prove hazardous to the individual as well as the public.

METHODS

Retrospective data of 38 professional drivers referred to the neuro ophthalmology department was reviewed and assessed.

RESULTS

Out of 38, 13 patients were found to have visually disabling ocular pathology which can prove to be dangerous while driving.

CONCLUSION

The study gives an insight to the fact that we need a thorough knowledge, examination standards, protocols and better coordination among Physician, Ophthalmologists and the State to determine whether an individual is functionally fit to drive or not.

INTRODUCTION

The decision to recommend a license for driving is an important one. It equates to freedom, independence and in many cases economic livelihood for the patient. But if the recommendation is based on an incorrect assessment, it may prove hazardous to the individual as well as it may compromise public safety. Neurological disorders can compromise a person's driving fitness. However, the complexity of these disorders – and the subjective nature of evaluations – can make determining driving fitness difficult.

As an Ophthalmologist, we need to be more vigilant as many visually disabling diseases can be easily missed in a routine ophthalmological examination. Unfortunately, there seems to be little consensus among health professionals, driving experts, and state government on how to advise these individuals. Despite being an issue of such massive impact, there are very few studies addressing the need for an elaborative workup before issuance of driving license. The aim of this study was to have an insight on the ocular status of the professional drivers, who, if given a driving license without proper assessment and regular review, can pose a serious public health problem.

METHODS AND MATERIALS

This is a single centre retrospective study which included professional drivers by purposive sampling who came to the outpatient department of Aravind Eye Hospital, Madurai for ophthalmological check-up either for issuance or renewal of driving license or with some other symptom in a period of 3 months i.e. January to March 2017.

All patients received a comprehensive ocular examination which included Best Corrected Visual Acuity, Intraocular Pressure (by non-contact tonometer), Binocular Single Vision (by Worth four dot test), Colour vision (by Ishihara plates), central fields (by Bjerrum tangent screen), slit lamp examination of anterior segment and fundus examination (by 90 D lens). Out of these, the patients who had specific ocular pathology were referred accordingly to various speciality clinics. We further analysed the data of the patients who were referred

to neuro ophthalmological department. There were 38 such patients who underwent further examinations and investigations based on their symptoms and findings of initial examination.

RESULTS

Out of a total of 2677 professional drivers who came to the OPD, 38 were referred to the neuro ophthalmological department of Aravind Eye Hospital, Madurai.

All 38 drivers were males. The mean age of the drivers was 48.29 ± 7.37 years.

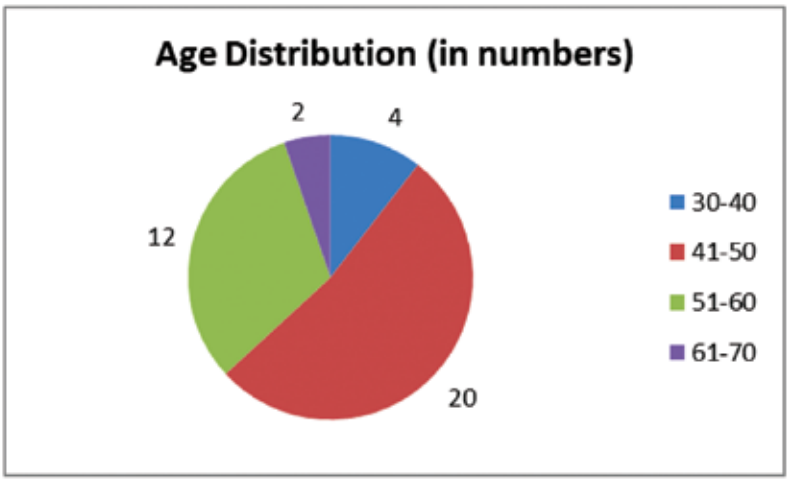

Fig. 1: Pie chart representing age distribution among the drivers

Symptomatology

Table 1. Number of drivers presenting with specific complaints

Presenting complaints	Number
Sudden decrease of vision/field	7
Intermittent squinting	1
Drooping eyelids	1
Diplopia	1
Glare	1
Issuance/Renewal of license	27

Out of these, 13 patients were found to have ocular pathology which can prove to be hazardous while driving.

Table 2: Case-wise details. N: Normal, D: Defective, NA: Not Assessable, +:Present, DM: Diabetes Mellitus, HTN: Hypertension, IHD: Ischemic Heart Disease.* without glass ** with HFA

	Chief complaint	BCVA		CV	CF	BSV	Diagnosis	Systemic Co-morbidity	Special investigations
		RE	LE						
1	Sudden defective vision	6/60	6/60	D	N	+	BE Toxic neuropathy (Ethambutol)	TB	MRI-Noncompressive optic neuropathy VEP Prolonged P100 latency
2	Intermittent squinting	6/6	6/6	N	N	+	Ocular Myasthenia	Nil	Ice Pack test +ve
3	Drooping of lids	6/6	6/6	N	N	+	Ocular Myasthenia	DM	Ice Pack test +ve
4	License renewal	6/9	1/60	N	LE Peripheral constriction *	+	LE Aphakia	DMHTN	Nil
5	Diplopia on left gaze	6/6	6/6	N	N	Diplopia	Left LR palsy	DMHTN	Nil
6	Defective Field of vision	6/6	6/9p	N	Right Homonymous Hemianopia **	+	Right Homonymous Hemianopia	HTNIHD	CT Brain-Sub acute lacunar infarct in optic radiation
7	Sudden defective vision, trauma	5/60	6/6	D	D	+	Traumatic optic neuropathy	Nil	CT orbits-Intraconal hematoma
8	License issuance	6/6	3/60	N	N	Left suppression	Left High Myopia, Anisometropic amblyopia	Nil	Nil
9	Glare	6/6	6/60	N	N	+	LE corneal scar with ALC tear	Nil	Nil
10	Inability to move hand to a specific object	6/18	6/36	N	D	+	Optic Ataxia	DMHTNIHD	MRI Brain- B/L Occipito-parietal infarct
11	Sudden defective vision	2/60	6/6	D	D	+	Optic Neuritis (Multiple Sclerosis)	Nil	MRI-Brain-Paraventricular demyelinating plaque
12	Sudden defective vision	HM	6/6	D	D	NA	NAION	DM	Nil
13	Sudden defective vision	6/6	1/60	D	D	NA	NAION	HTN	Nil

DISCUSSION

In our study, we specifically report the incidence of neuro ophthalmological diseases in professional drivers. We believe that as compared to ocular diseases like glaucoma, diabetic retinopathy which receive wide awareness and frequent screening camps, neuro ophthalmological disorders are hardly screened for or recognised. But the symptoms caused by these diseases like diplopia can prove to be very dangerous while driving.

Several studies have concluded that there is no significant association between eye diseases like cataract, glaucoma, macular degeneration, diabetic retinopathy and motor vehicle collision involvement rates.[1,2,3,4] However, the neurological impairment (multiple sclerosis, Parkinson disease or a stroke) is associated with increased risk for all types of road accidents.[1,2,4]

In India, there are no well-defined rules for the practitioner in the contentious issue of reporting unsafe drivers to a public health authority. In our study, we report 13 such patients with ocular pathology which can severely impair driving function. Shouldn't there be mandatory reporting laws for any unsafe driver with a pathology that can risk the life of the individual as well as the public? The practitioner may be conflicted in a situation where he or she suspects the individual is driving against advice.[5] However, there are several concerns that need to be addressed regarding reporting, particularly involving trust between physician and patient. Whether to violate the trust that is an essential and moral feature of the doctor-patient relationship or to protect the society from risk of serious harm is a sensitive issue.

The ethical shades of grey become even more blurred in instances where the reporting means snatching the livelihood from an individual even though he is not involved in a direct crime. Adequate compensation for lost working days or rehabilitation should be available to drivers who suffer from ocular disorders that restrict them from driving. This will not only aid in increasing the involvement of a physician but also encourage the self reporting to the licensing bureau by the drivers of their disabilities.

Also, in a country like India, where mandatory reporting is not required, there is little protection for the doctor who chooses to report any such event out of concerns for public safety. Perhaps anonymous reporting or legal protection of the reporting physician could help

the situation as concerns over the potential for litigation likely leads to underreporting to authorities.

Various manifestations of vision impairment have been identified that place older drivers at higher risk for accidents, most notably including severe visual-field loss and a restricted useful field of view (UFOV).[6,7] Some research suggests that diabetes[8] or anti-diabetic medication use[9] is associated with an increased motor vehicle collision risk, while other studies have documented increased accident involvement among those with heart disease[10] or those with greater orthostatic systolic blood pressure drop.[11]

In our study, we observed that the incidence of neurological diseases was more in the age group above 50 and in patients with associated comorbidities like diabetes, hypertension, ischemic heart disease etc. These middle aged drivers with possibilities of comorbidities can have any acquired ocular disease at any point of their driving career. The licensing bureau should take these facts into consideration and hence, the follow up and the time interval for renewal of licence should be customised for drivers based on their age and systemic profile.

Both primary care and subspecialty physicians often lack basic knowledge and formal training to make a recommendation on who can safely operate a motor vehicle.[12] Furthermore, despite published guidelines for assessing driving competency, many physicians are often unaware of the laws in their state.[13] Certifying physicians should be adequately trained to assess the fitness based on rules and regulations of their region.

Furthermore, all health care reports should be available to every treating surgeon or physician so as to enable a tailored assessment for every person.

The limitation of this study includes small sample size and time period. However, the aim of the study is to give an insight to the fact that we need a thorough knowledge, examination standards and protocols and better co-ordination among physician, ophthalmologists and the state to determine whether an individual is functionally fit to drive or not.

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Prescribing Pattern Of Topical Antibiotics In Ophthalmology - Are We Doing It Right?

Dr. Rosina Thomas

ABSTRACT

CONTEXT

A wide range of potent topical antibiotics are now at the disposal of each Ophthalmologist and they are being prescribed indiscriminately.

AIMS

To assess the trends in prescribing topical antibiotics for ocular surface infections and pre and post operative prophylaxis among Ophthalmologists in Kerala and to analyse whether they are in line with evidence based recommendations

SETTINGS AND DESIGN

Prescription pattern of topical antibiotics among Ophthalmologists in Kerala were surveyed by mail or by interviews using a questionnaire. The responses were statistically analysed and compared with current recommendations.

RESULTS

The 112 Ophthalmologists who participated in the survey dispensed a mean of 14.8 (range 1-60) topical antibiotic prescriptions in a day. The commonest indication for a topical antibiotic was infective conjunctivitis (67%) followed by pre and post operative prophylaxis (23.3%). The most popular topical antibiotics prescribed were Moxifloxacin (30.4%), Ofloxacin (25.6%) and Ciprofloxacin (18.8%). 81.2% of participants believed that majority of cases of infective conjunctivitis were mild and self limiting. 82.2% among them would prescribe a topical antibiotic for them. 92% of surgeons

prescribed a topical antibiotic preoperatively and it was Moxifloxacin in 47.35% cases.

CONCLUSIONS

Though 81.2% of participants believed that majority of cases of infective conjunctivitis were mild and self limiting, 82.2% of them would still prescribe a topical antibiotic. Preoperative antibiotics are used by 92% of surgeons, though no conclusive evidence supports the same.

KEY WORDS

Antibiotics, conjunctivitis, fluoroquinolones

KEY MESSAGES

Rampant and injudicious use of topical antibiotics, especially fourth generation fluoroquinolones like Moxifloxacin raises the possibility of emergence of drug resistance. New rational and evidence based guidelines need to be formulated on the prescribing pattern of topical antibiotics in the community which are practical and cost effective

INTRODUCTION

In developing countries like ours, acute infectious conjunctivitis is a common presentation to general practitioners in the primary care setting.[1] It is also the commonest condition managed by Ophthalmologists. A wide spectrum of topical antibiotics is now available to each practitioner. But the current practice of prescribing broad spectrum topical antibiotics by Ophthalmologists raises serious concerns. The aim of the study was to assess the trends in prescribing topical antibiotics for ocular surface infections and pre and post operative prophylaxis among Ophthalmologists in Kerala and to analyse whether they are in line with evidence based recommendations.

SUBJECTS AND METHODS

Prescription pattern of topical antibiotics among Ophthalmologists in Kerala were surveyed by an internet based survey tool (Sogo Survey). Invitations to take part in survey were sent via email. Interviews using a printed questionnaire were conducted for Ophthalmologists who were not accustomed to online methods of survey.

The responses were recorded and statistically analysed. Statistical analyses were performed using SPSS Version 16.0. Results of categorical variables were reported as count and percentages. The differences between categorical variables were analyzed using the nonparametric

test-Fisher's exact Test. P value <0.05 was considered as significant for all comparisons. The results were compared with current recommendations.

RESULTS

A total of 112 Ophthalmologists participated in the survey. 42 (37.5%) among them practiced in Government Institutions, whereas the rest 70 (62.5%) worked in private hospitals or clinics.

Thirteen (11.6%) of participants worked in Primary care institutions, 34 (30.4%) in Secondary care and 65 (58.0%) in Tertiary care centres.

Among the 112 participants in the study, 51 (45.5%) were General Ophthalmologists, 22 (19.6 %) were Trainee Ophthalmologists and 39 (34.8%) were Super-specialists.

On an average, they dispensed 14.8 (range 1-60) topical antibiotic prescriptions in a day. No statistical correlation could be found with the number of antibiotic prescriptions in a day and the number of years of clinical experience of the Ophthalmologist or with the number of patients seen in the OPD in a day.

The commonest indication for prescribing a topical antibiotic was infective conjunctivitis (75, 67%) followed by pre and post operative prophylaxis (26, 23.2%) and cases of non-specific red eyes (11, 9.8%).

Among all categories of Ophthalmologists, the most commonly prescribed topical antibiotic was Moxifloxacin (30.4%), followed by Ofloxacin (25.6%), Ciprofloxacin (18.8%), Tobramycin (12.5 %), Chloramphenicol (10.7%) and Gatifloxacin (1.8%). Those in Government hospitals prescribed more of Ciprofloxacin and Tobramycin whereas Ofloxacin and Moxifloxacin were more used in private institutions. Primary care physicians used Ciprofloxacin, Tobramycin and Chloramphenicol more frequently than those in secondary and tertiary care. [Table-1]

Table 1. Commonest antibiotic prescribed and type of health care institute

Topical antibiotic Prescribed	Health care institute		P value
	Govt. Hospital	Private Hospital	
Ciprofloxacin	20	1	
Ofloxacin	0	29	
Moxifloxacin	0	34	<0.001
Tobramycin	12	2	
Gatifloxacin	1	1	
Chloramphenicol	9	3	

Among the 112 participants, 68 (60.7%) agreed that most cases of acute infective conjunctivitis in the adult population were viral and self limiting. Ninety one (81.2%) believed that majority of cases of bacterial conjunctivitis were mild and self limiting, whereas 21 (18.8%) thought they progressed to complications if untreated.

In cases of uncomplicated viral conjunctivitis, 92 (82.2%) would prescribe an antibiotic. Forty four (39.3%) participants would always prescribe a topical antibiotic, 48 (42.9%) would do so occasionally, but 20 (17.9%) would never. [Table 2], [Table 3]

Table 2. Frequency distribution of usage of topical antibiotic for uncomplicated viral conjunctivitis

	Frequency	Percent
Yes	92	82.14
No	20	17.85
Total	112	100

Table 3. Knowledge action mismatch

Most of acute infective conjunctivitis cases are mild and self limiting	Usage of Topical Antibiotic for Uncomplicated Conjunctivitis		P value
	Yes	No	
Agree	63	5	0.001
Disagree	29	15	

One hundred and two (91.1%) Ophthalmologists would advice an antibiotic for a case of bacterial conjunctivitis, 10 (8.9%) would not. A topical antibiotic was used by 96 (85.7%) participants in non specific red eye and by 45 (40.2%) in non–infective conditions like allergic conjunctivitis, subconjunctival haemorrhages, dry eyes and corneal degenerative conditions.

In cases of infective conjunctivitis, 101 (90.2%) participants would prescribe a topical antibiotic at the first visit, rather than wait and watch for the emergence of complications. The advantages of initiating topical antibiotic therapy according to the participants were symptomatic relief (21.4%), shortened course of infection (66%) and reduced chances of recurrence and transmission (1.8%). 10.7% of participants thought that a topical antibiotic would worsen symptoms by causing surface toxicity.

Topical antibiotics were usually prescribed less than four times a day by four (3.6%), four times a day by 59 (52.7%) and more than four times a day by 49 (43.7%). [Table 4]

Table 4 Frequency of topical antibiotic administration in infective conjunctivitis

Prescription of an antibiotic	Frequency	Percent
<4 times/ day	4	3.6
4 times/ day	59	52.7
>4 times/ day	49	43.7
Total	112	100

Sixty four (57.1%) of the participant Ophthalmologists took time for patient education, whereas 48 (42.9%) did not.

Fifty six (50%) of respondents believed that the use of a topical antibiotic preoperatively can prevent a postoperative intraocular infection, 11 (9.8%) did not think so and 45 (40.2%) were unsure. 92% of surgeons routinely prescribed a preoperative topical antibiotic whereas 8% did not. The first choice of preoperative antibiotic was Moxifloxacin (47.3%), followed by Ofloxacin (42%) and Gatifloxacin (9.8%).

DISCUSSION

According to the present survey, infective conjunctivitis (67%) was the most common indication for the prescription of a topical antibiotic among Ophthalmologists in Kerala, practicing in both Government and private institutions and at all levels of medical care. It was managed by all participants from trainee Ophthalmologists to super-specialists and with varying years of clinical experience.

70% of cases of acute infectious conjunctivitis in the adult population are viral in aetiology. It is usually caused by adenovirus infection. It is a self limiting condition that usually resolves within two weeks of onset of symptoms. There is no evidence supporting the use of anti-viral medication and their efficacy has not been proven.[1] Though 60.7% of the Ophthalmologists were aware of these etiological factors and the natural course of the condition, 82.2% of them would still prescribe a topical antibiotic for a patient with viral conjunctivitis.

Bacterial conjunctivitis is commonly due to infection with *Haemophilus influenzae, Streptococcus pneumoniae or Staphylococcus aureus.*[2] A Cochrane systematic review found that acute bacterial conjunctivitis is often a self limiting condition, 65% patients treated with placebo showed significant improvement. Patients treated with a broad spectrum

topical antibiotic had improved microbiological and clinical outcome, especially when treated early (days 2 to 5). The use of antibiotics speed recovery, reduce relapse and transmission and may prevent important sight threatening complications. But the risk of adverse events in those treated with placebo was also found to be low1. 91.1% of participants would prescribe a topical antibiotic for bacterial conjunctivitis, whereas 8.9% would not.

A diagnosis of conjunctivitis is usually made on the basis of a clinical history and examination. Since at times it is difficult to differentiate between infective and non- infectious conjunctivitis. So, for a presumed case of infective conjunctivitis, most practitioners prescribe a broad spectrum topical antibiotic on an empirical basis without culture.[3,4] Patients are instructed to seek follow-up care if the expected improvement does not occur or if vision becomes affected. According to the present survey, 85.7% of participating consultants would prescribe a topical antibiotic for a case of non specific red eyes. Antibiotic eye drops were also injudiciously used for non infectious conditions like allergic conjunctivitis, subconjunctival haemorrhages and non-infective corneal pathologies by 40.2% of Ophthalmologists.

Fluoroquinolones are currently the most popular broad spectrum antibiotics for treatment and prophylaxis of eye infections because of their safety, excellent penetration into the aqueous and vitreous, long duration of tear concentration, and broad spectrum of antimicrobial activity. An increasing number of guidelines recommend avoiding the use of fluoroquinolones and combinations except for the most severe infections or following treatment failure.[7] But in Kerala, fourth generation fluoroquinolones like Moxifloxacin are rampantly prescribed for uncomplicated infective conjunctivitis and non- infective conditions, more so in private institutions.

Participating Ophthalmologists prescribed a topical antibiotic for a patient with infective conjunctivitis in the belief that it would lessen the patient's symptoms, reduce duration of infection and chances of recurrence. Though these advantages have been proven by numerous studies, they come at the cost of worsening surface toxicity and increased risk of developing drug resistance.[6]

A large proportion of Ophthalmologists (90.2%) prescribed a topical antibiotic empirically at the time of diagnosis for an acute simple infective conjunctivitis, rather than wait and watch (9.8%) for the emergence of complications. A better option that has been recommended is to delay treatment for 5 days and prescribe antibiotics if no improvement.[5]

The usual factors that influenced the choice of topical antibiotic in most of practicing Ophthalmologists in Kerala were local availability of drugs, cost of drug and affordability of the patient, rather than knowledge of etiological factors and drug sensitivity of the infecting organisms. Promotion by pharmaceutical companies rarely influenced the participants.

The American Academy of Ophthalmology suggests a 5 to 7 day course of a broad spectrum topical antibiotic, which is the most convenient or least expensive one usually available, since there is no clinical evidence suggesting the superiority of any particular antibiotic in simple bacterial conjunctivitis.[7]

The practice of prescribing topical antibiotic for infections at frequencies more than or less than the recommendation of four times a day by 47.3% of consultants and tapering of antibiotics should be avoided to prevent generation of drug resistance. Compliance with the length of time (7-10 days) the antibiotics are prescribed for is also particularly important.

The economic impact of infective conjunctivitis is also substantial. Preventive infection-control measures by good personal hygiene and patient education can be extremely cost-effective. But in routine busy clinical practice, 42.9% of participating Ophthalmologists do not bother to take time for patient education, which is the only proven method of disease control.

A qualitative study of patients' perceptions of acute conjunctivitis performed in the UK[8] revealed that most patients when informed about the self limiting nature of the disease were satisfied without antibiotic prescription. So whenever an infection of viral aetiology is suspected, the emphasis should be on patient education regarding its self-limiting nature, thus avoiding thousands of unnecessary antibiotic prescriptions every year.

Moreover, treatment of all red eyes with topical antibiotics can result in a delay and confusions in the diagnosis of other more severe and urgent non infective conditions.

Though extensive research has been done, the only two prophylactic methods proven to be effective in postoperative endophthalmitis prevention are antisepsis and intracameral injection of 1 mg cefuroxime at the end of the surgical procedure.[9] Though 50% surgeons were aware of the futility of a preoperative antibiotic, in their endeavour to avoid the worst catastrophe, 92% of them would prescribe a pre-

operative topical antibiotic, which is usually a fourth generation fluoroquinolone (57.1%). Resistance to the fluoroquinolone with Staphylococcus isolated from endophthalmitis has been shown to be due to topical surgical prophylaxis, especially for prolonged periods.

The other possible causes of emerging resistance to topical antibiotics as suggested by the participants were indiscriminate prescription of highly potent antibiotics, irrational use of combinations of antibiotics with steroids and NSAIDs, prescription of topical antibiotics by general practitioners and other specialists and over the counter sale of topical antibiotics.

Recent reports of fluoroquinolone resistance with Staphylococcus[10] and Pseudomonas which is more common with the second (ciprofloxacin and ofloxacin) and third generation (levofloxacin and purified ofloxacin) than by a fourth-generation fluoroquinolone (moxifloxacin and gatifloxacin) could emerge as a major therapeutic challenge. As of yet, the problem is not a public health issue, since drug resistance may be due to antibiotic over use rather than patient-to-patient spread.

The current practice of prescribing broad spectrum topical antibiotics by Ophthalmologists in Kerala raises concerns of antibiotic resistance, cost-effectiveness, and potential increase in complications due to antibiotic use. Rampant and irrational treatment of infective conjunctivitis and other non-infective conditions with antibiotics, inappropriate dosing regimen and prolonged duration of therapy should be checked. Use of highly effective fourth generation fluoroquinolones like Moxifloxacin should be judicious and reserved for most severe cases. New rational and evidence based guidelines need to be formulated on the prescribing pattern of topical antibiotics in the community which are practical and cost effective, with more emphasis on preventive aspects and patient education.

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This Paper was conferred with the **AIOS - APOS K VENGALA RAO AWARD** for the **BEST PAPER** of **COMPREHENSIVE OPHTHALMOLOGY** Session.

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Novel Inverted Telescope-TNO Test System Compared With The Nidek Projector Chart (CP690) To Assess Distance Stereopsis.

Dr. Mihir T Kothari

INTRODUCTION

High grade stereopsis is the function of bifoveal fusion. Presence of fine stereopsis [stereoacuity < 40" (seconds of arc) on TNO test] essentially confirms an efficient and 'normal' binocular input.[1] Measurement of Stereoacuity is found useful in:

1. Monitoring the control of ocular alignment in intermittent strabismus[1,2] viz. the intermittent exotropia,[3-5] the intermittent esotropia[1] and accommodative esotropia.[6]
2. Evaluating the functional outcome of strabismus surgery.[7]
3. Comparing the effects of early intervention in infantile strabismus syndromes viz. congenital esotropia.[8]
4. Screening of amblyogenic factors in children viz. anisometropia, significant ametropia and strabismus.[9]

In a strabismus clinic, measurement of distance stereopsis is particularly useful in the management of intermittent exotropia and esotropia of divergence paralysis type. This is mainly because reduction in the distance stereopsis is a sensitive sign of early deterioration of these strabismic disorders and generally makes a case for the surgical intervention.[10]

Various tests have been used for the measurement of stereoacuity for the near.[11] Titmus/Wirt Fly test, Randot test and TNO test are among the more popular ones. For the distance stereopsis, the Mentor BVAT SG[12] and Frisby Davis distance stereo test (FD2)[13] are fairly accurate and versatile. However, the distance stereoacuity tests are not commonly available in the clinics and they are relatively expensive.

In the past, we had demonstrated that TNO test, that uses red-green random dot stereopairs (anaglyphics), can be combined with an inverted binocular telescope to measure the global, crossed disparity induced, central stereopsis.[14]

The present study was done to find 1) whether the presence of distance stereopsis on CP 690 chart could be predictive of presence of stereopsis on Inverted telescope-TNO system, 2) to assess the effect of increasing anisomyopia on distance stereopsis on CP 690 chart and 3) to find the magnitude of anisometropia that lead to loss of stereopsis on both CP 690 and Inverted telescope-TNO system.

METHODS

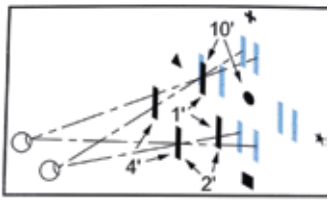
This prospective cohort study was carried out in a standalone Pediatric Ophthalmology and Strabismus tertiary teaching eye centre in the Western India. The orthophoric subjects having the best corrected vision of 6/6 in each eye within the age group of 10-45 years, were included in the study. A pediatric optometrist performed complete ophthalmic examination. Ocular motility evaluation was reconfirmed

by a fellowship trained strabismologist. Once the subject was diagnosed as 'normal', an oral consent was obtained explaining the nature of the test and the need of the study.

The eligible subjects were tested first on a standard distance stereopsis chart using polaroid lenses and CP 690 projector chart (NidekInc, Japan) calibrated for 6 meters distance. This was followed by a repetition of the test with increasing anisomyopia (induced by introducing + lenses in the steps of 0.5 DS) in front of the left eye.The responses were recorded as per the following stereopsis values.

<Minute stereo>

The four bars look closer than the center dot. The left bar is closest and the bottom, right and top are in sequence. The difference of convergence angles (the heights of each step) between the left and the bottom bar is 4', bottom - right: 2', right - top: 1', and top - dot: 10'.



On the TNO test (TNO institute of Vision, Netherlands). Care was taken to hold the TNO chart at 40 cm (measured with a tailor's tape) in a brightly lit room by the same investigator in the same room conditions each time. The subjects were allowed enough time to recognize the 3 dimensional image in the test. Once the subject could appreciate the stereopsis, a binocular telescope (Galilean design, 26 mm, 2X, Camma Inc. China) was held in an inverted fashion in front of the red-green goggles by the subject. The inter pupillary distance (IPD) was adjusted by the subject, the test was run again and the response was recorded in the same fashion. Care was taken to maintain the test distance at 40 cm and the subjects were given enough time and explanations to complete the test. This was followed by a repetition of the test with increasing aniso myopia (induced by introducing + lenses in the steps of 0.5 DS) in front of the left eye. The stereopsis was not graded on the TNO test. Only first 3 plates were utilized.

RESULTS

10 adults aged 30.6 years ±10(10-42) of which 4 were males were included. All the patients had full stereopsis (1") on distance CP 690 chart. With fogging, the stereopsis was abolished completely at + 3 DS in front of the left eye. Lower levels of blur +0.5 DS to +2.5 DS was apparent as a blur but was unable to degrade the stereopsis on CP 690 chart.

All the patients who had stereopsis on CP 690 chart also had stereopsis on Inverted Telescope-TNO Test system. On that chart also, the subjects lost stereopsis at +3.0 DS giving 100% correlation with CP 690 chart. Lesser amount of induced anisometropia was not associated with the loss of stereopsis.

DISCUSSION

The TNO test is a popular test used to assess the near stereoacuity. In this test red-green anaglyphics are presented in a random dot stereopair. When viewed with the Red-Green filter (goggles) it induces the stereo effect that measures the global, central, crossed disparity threshold (central stereoacuity). Inversion of the chart (upside down) can test the stereoacuity for the uncrossed disparity. The advantages of TNO test over Titmus/Wirt fly test are two folds. 1) There are no monocular clues and 2) Red-Green colour optimizes the stereo contrast for the measurement (akin to the measurement of the Cone function with Photopic conditions the optimisation of Cone system)

By definition, stereoacuity is the smallest depth difference we can see, that is, a depth discrimination threshold. Thus stereoacuity can be thought of as the "resolving capacity" of stereopsis, much as visual acuity in the resolution limit of the spatial vision. In other words it is the measure of the horizontal binocular disparity that results from the images in each eye being formed on the closely spaced non-corresponding retinal points within Panum's fusional area. This disparity can be measured[16] using the formula $n=2ax/d^2$, where n is the angular stereo disparity in radians (to get the stereoacuity in arc seconds mulitply with 2,06,256), 2a is the inter pupillary distance (IPD), d is the fixation distance and x is depth interval. The fixation distance in the inverted telescope distance can be calculated using the formula $u = 1/v$ independently for each lens of the telescope (eye piece and the objective lens). The image of the first lens acting as the object for the second. Once the fixation distance is calculated, stereoacuity can be derived by measuring the IPD. The disparity value can also be calculated for any distance by multiplying the original value on TNO test chart by a factor 40/d, where d is the viewing distance in cm.[17]

There are a few limitations of the TNO test. 1) It dissociates eyes, 2) it induces crowding phenomenon that reduces the visual acuity in the amblyopic eye more severely and there by reducing the stereopsis, 3) TNO test induces colour rivalry between the two eyes and 4) the test produces chromatic aberration. These are also some of the reasons

why the stereoacuity norms on TNO test are different (lower) than that with Titmus/Wirt Fly test.

Similarly each of the distance Stereoacuity tests have their limitations and merits. We do believe that an inverted telescope system can be used with any other near stereoacuity chart. However, the test would need to be standardized, normative values need to be calculated and the repeatability needs to be assessed. So long as one is consistently using the same stereoacuity chart, the interpretation would remain the same.

The effect of pictorial monocular clues was eliminated by the use of random dots and the use of telescopic system. However, the effect of convergence and accommodation though less likely to be clinically significant, may affect the measurements.

In the past the investigators have reported a graded reduction on near stereopsis and binocular vision (fusion) per diopter of induced anisometropia.[18] Anisomyopia was found to be more degrading than the anisohyperopia and +3 DS blur (causing anisomyopia of 3 DS) was associated with complete loss of stereopsis.[19]

In the present study we found presence of stereopsis on CP 690 was predictive of presence of stereopsis o inverted Telescope-TNO chart. However, there was no graded reduction of stereopsis on distance stereopsis using CP 690 chart. 3 D of indued anisomyopia was universally associated with loss of stereopsis.

In conclusion, novel inverted telescope-TNO system works well to assess presence or absence of distance stereopsis. 3 D of anisomyopia can be potentially very damaging to the distance stereopsis. Lower levels of anisomyopia is compatible with intact stereopsis.

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This Paper was judged as the **BEST PAPER** of **CORNEA I** Session.

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Ocular Metastasis In Eye Donors With Systemic Malignancy

Dr. Shivani Nayak, Dr. Rekha Gyanchand, Dr. Jyotirmay Biswas, Dr. Kaustubh Mulay

ABSTRACT

PURPOSE

To analyze the presence of gross or microscopic metastatic cells in ocular tissue with systemic malignancy.

METHODS

A prospective study of 103 eyes from 52 donors who donated eyes to the eye bank and whose cause of death was malignancy with metastasis studied. Details pertaining to malignancy were checked from the hospital medical records of the donor. After gross and slitlamp examination, the eyes were preserved in formalin for histopathological study.

RESULTS

Most common primary cancer in our study was leukemia and CNS malignancies (11.53%). On gross/slitlamp examination,1 pair of eyes from testicular carcinoma had abnormal infiltrates in uvea and 1 pair from promyelocytic leukemia had abnormal infiltrates in optic nerve. On microscopic examination, 5 eyes (4.58%) had malignant cells of which 2(1.94%) were in choriocapillaries, 2(1.94%) in ciliary body and 1(0.97%) in choroid.

CONCLUSION

The incidence of corneal metastasis with active solid carcinoma is nil. The most common site of intraocular metastases is uvea.

KEY WORDS

Ocular metastases, systemic malignancy, eye donors.

INTRODUCTION

In an eye-bank 30-40% of eye donations are procured from donors with cancer as the cause of death, especially in an urban setup. Most eye bank associations, due to the potential risk of transmission of diseases through corneal transplantation, consider malignancies to be a contraindication for keratoplasty.[1] There is a significant difference between the number of corneas needed for treating corneal blindness and the number of corneas procured,[2] especially in india. If eyes from patients dying of cancer can be used for transplantation without fear, then it can help to reduce the shortage of donor corneas and in turn number of corneal blindness. Hence this study was planned.

OBJECTIVES

- **Aim**

Histopathological examination of ocular tissue to rule out ocular metastasis from donors with systemic cancer as cause of death.

To analyse the following

- Presence or absence of tumor cells in ocular tissue by histopathologic examination in cancerous donors.
- To identify commonest site of microscopic malignant cell deposits in the eye.

METHODOLOGY

One year descriptive cross sectional study of 103 eyes of 52 patients with systemic malignancy

INCLUSION CRITERIA

Enucleated eyes from donors diagnosed with cancer, either solid or haematological, were accepted.

EXCLUSION CRITERIA

- Keratitis
- Phthisis bulbi
- Disorganized globe

After enucleation, the eyes were subjected to gross examination, detailed slit lamp evaluation and histopathological analysis. Those that had a high index of suspicion of malignancy on microscopy were subjected to immuno-histo-chemistry (ihc) for confirmation.

RESULTS

The data obtained was analyzed and the final observations were tabulated as below. The statistical analysis was performed by stata 11.2 (College station tx USA).

During the period of study, the total number of eyes collected in our eye bank was 1398 and 103 eyes were obtained from donors with a history of systemic malignancy. This constituted 7.36% of the donated eyes. In this study most of the donors were of the age between 61 to 80 years (53.84%) and followed by 41 to 60 years (28.84%). The mean age was 61.43 ± 14.68 years (range : 25 to 87 years). In the present study 51.93% of the donors were females and 48.07% were males. The male to female ratio was 0.92:1.

36 Patients out of the 52(69.23%) had been diagnosed of cancer 1-5 years before their death. The mean duration of malignancy, i.e; the duration from diagnosis of malignancy to death was 2.37 ± 2.05 years. (Range: 15 days to 9 years).

51.92%(27) among the 52 donors had metastases to some organ. Among them, the most common site of metastases was to the lung in 11.54%, followed by liver in 9.61% and peritoneum (7.69%). Abdominal metastasis in total was present in 9 donors (17.03%). 5 donors had multi-organ metastases which included 2 patients with a cervical lymph node involvement amongst them. 25 donors (48.07%) did not have any metastases. In the present study among the 52 donors examined, 7 patients (13.46%) had head and neck region metastases of which the most common site of metastases was to the cervical group of lymph nodes in 6 donors (11.53%) and 1 patient (1.92%) had metastasis to the brain (primary-ovary). The most common primary malignancies causing the metastases to head and neck region were: brain(2) and 1 each from thyroid, lung, stomach, ovary and testis.

Among the total number of 52 donors, 9 people had not received any form of treatment for their primary condition. Among the people

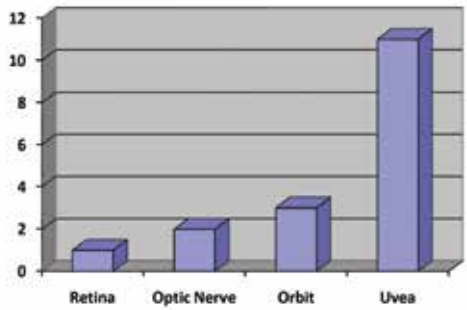
who received treatment of some form, the mean duration of treatment received was 19.06 ± 16.92 months. (Range: 15 days-6 years). Only 5 (9.61%) among the donors had received some treatment for their primary malignancy in the previous 1 month.

Table 1. shows the distribution of primary malignancies in eye donors

Primary Malignancy	Distribution (n=52)	
	Number	Percentage
Hematological Malignancies		
Leukemias	06	11.53
Hodgkin's Lymphoma	03	05.76
Non-Hodgkin's Lymphoma	02	03.84
Multiple Myeloma	01	01.92
CNS Malignancies		
Brain tumors	06	11.53
Breast Malignancies	02	03.84
Bone Malignancies	01	01.92
Gastrointestinal Malignancies		
Esophageal Carcinoma	04	07.69
Gall Bladder Carcinoma	01	01.92
Pancreatic Cancer	02	03.84
Stomach Cancer	02	03.84
Colorectal Cancer	02	03.84
Urogenital Malignancies		
Renal Cancer	02	03.84
Testicular Cancer	04	07.69
Prostate Cancer	02	03.84
Uterine Cancer	01	01.92
Ovarian Cancer	03	05.76
Lung Cancer	03	05.76
Laryngeal Cancer	01	01.92
Thyroid Cancer	03	05.76
Maxillofacial Cancer	01	01.92
Total	52	100

Table 2 showing: distribution of gross ocular abnormalities		
Gross abnormalities	Distribution (n=103)	
	Number	Percentage
Iris-Choroid	02	01.94
Optic Nerve	02	01.94
No Gross Abnormality	99	96.12
Total	103	100

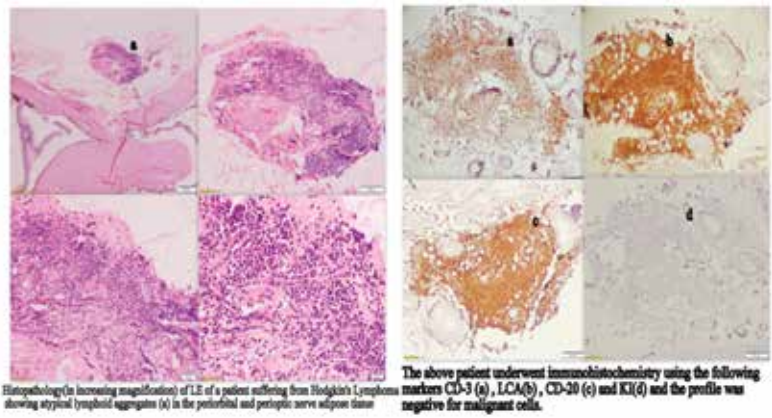
Bar diagram 1 showing distribution of microscopic ocular changes



In 1 patient with a testicular cancer, only the retina of the left eye showed a peripheral retinal inflammatory infiltrate.

In 1 patient with acute promyelocytic leukemia, the optic nerve of 1 eye showed the presence of abnormal mononuclear cell infiltrates. At the same time the orbital tissue of the same patient showed perivascular infiltration of similar looking mononuclear cells.

In a patient with a non-hodgkin's lymphoma, there were atypical lymphoid cell aggregates noted in the periorbital fat tissue as well



Histopathology(in increasing magnification) of LE of a patient suffering from Hodgkin's Lymphoma showing atypical lymphoid aggregates (a) in the periorbital and perioptic nerve adipose tissue

The above patient underwent immunohistochemistry using the following markers CD-3 (a), LCA(b), CD-20 (c) and KI(d) and the profile was negative for malignant cells.

Image 1 (left) shows the microscopic photograph of atypical lymphoid aggregates and image 2 (right) shows immunohistochemistry negative for malignant cells

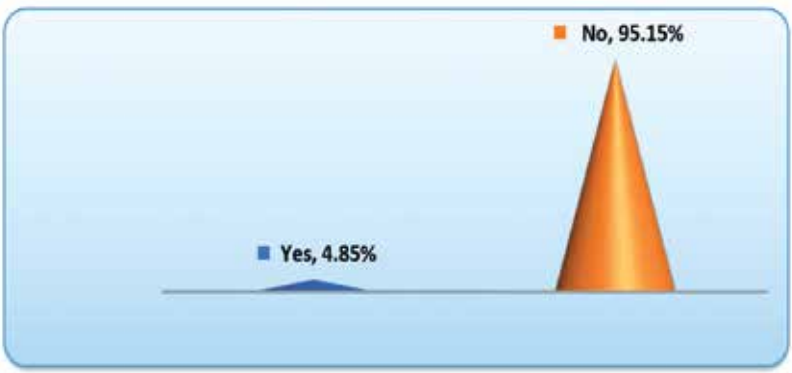
as the optic nerve of the left eye. But immunohistochemistry studies in all 3 cases confirmed that none of the cellular infiltrates in neither the retina, optic nerve nor the orbital tissue were malignant cells.

Table 3 shows the distribution of changes in the uvea noted on microscopic examination.

Gross abnormalities	Distribution (n=103)	
	Number	Percentage
Abnormal infiltrates in blood vessels	02	1.94
Autolytic changes in the choroid	01	0.97
Inflammatory infiltrates in the iris	02	1.94
Inflammatory cells in the cilia	01	0.97
Malignant cells in the choriocapillaris	02	1.94
Malignant cells in iris	01	0.97
Malignant cells in the ciliary body	02	1.94
No abnormality	92	89.32
Total	103	100.00

On microscopic examination of the uvea, abnormal infiltrates in blood vessels was seen in 2 eyes (1.94%), Abnormal spindle shaped cells were seen 2 eyes (1.94%), Inflammatory cells in the iris were found in 2 eyes (1.94%) and a single eye showed autolytic changes in choroid (0.97%). 5 eyes showed malignant cells in the uvea.

Bar diagram 2 shows the distribution of malignant cells among the donor specimens.



4.85% (5) of the total of 103 eyes examined were showing presence of malignant cells. Among them 2 eyes belonged to a patient having

an astrocytoma of the brain, 2 belonged to a patient having adenocarcinoma of the uterus and a 1 single left eye from a patient with testicular cancer showed the presence of malignant cells. All the malignant cells were seen in the uvea of the specimen eyes.

DISCUSSION

Cancer is the second leading cause of death in developed countries like united states of america[3] and it accounts for 20-25% of all deaths.[4,5,6] With the increasing number of deaths associated with cancer, there is a large pool of donors which can be used for corneal transplantation but are not being used at present. Literature in the past has shown transmission of malignancy in the recipient after corneal transplantation[7,8] which has caused a dilemma amongst corneal surgeons about the safety of using corneas obtained from donors dying of cancer.

But newer studies where corneas from patients dying of cancer have been used for transplantation and the recipients followed up for a long duration of time show no evidence of occurrence of the malignancy in the recipients.[1,9,10] In a developing country like India, with a very large number of cases of corneal blindness and the donor corneas being a scarce resource, every possible attempt to increase the size of the donor pool should be made. This present study was thus aimed at expanding the inclusion criteria of the eligible donor corneas.

In this present study, the histopathological examination showed that 05 (4.85%) of the total of 103 eyes examined were showing presence of malignant cells. Among them 2 eyes belonged to a patient having an astrocytoma of the brain, 2 belonged to a patient having adenocarcinoma of the uterus and a 1 single left eye from a patient with testicular cancer showed the presence of malignant cells. All the malignant cells were seen in the uvea of the specimen eyes. In a study conducted by Nelson et al, microscopic metastatic intraocular lesions were found in at least one eye in 5–10% of people dying of malignancy.[11]

These microscopic examination findings were consistent with previous studies which said the percentage of ocular metastases was between 4-7% (present study was 4.85%). The most common site for metastases noted in this study like previous studies was the uveal tract. Among the uveal tract we found that the most common sites were the choroid and ciliary body (40% each) followed by iris (20%). Other studies have noted that the choroid was the commonest site among the uvea in as many as 88% of cases.[12,13]

Table 4 showing comparison of similar studies				
	No. of donors with cancer	Most common primary malignancy	Ocular metastasis (No. of Eyes)	Most common site
Eliassi-Rad et al[14] (1976-80)	1043 (9.02%)	Lung(21.86%)	128(12.2%)	___
Nelson et al[15] (1973-1983)	358	Leukemia (32.68%)	66(9.3%)	___
Lopez-Navidad et al[1] (1999-2003)	204(34.7%)	Lung(18.8%)	4(1%)	Choroid(88%)
Present study (Dec. 2015-Dec 2016)	52(7.36%)	Leukemia (11.53%) Brain Tumor (11.53%)	5(4.85%)	Choroid (40%) Ciliary body (40%)

In the present study we found 4.85% of eyes with microscopic malignant cells infiltration. This is lower than reported in literature. Various studies have shown no transmission of cancer cells from donor to recipient. Barring lymphoproliferative disorders and primary malignancies of the eye, eyes obtained from other malignancies may be considered for transplantation as there are very few proven studies on cancer transmission from donor to recipient. Some limitations in our study were that specular study of the corneas obtained were not done. Ultrasound bio-microscopy of the angle was not done to look for any abnormal infiltrates.

CONCLUSION

Results suggest that ocular metastatic involvement in patients dying from active solid carcinoma is very low and transmission of malignancy is highly unlikely when there is no tumour infiltrate to the eye. Corneal donors with cancer represent a high percentage of corneas viable for transplantation. The results also suggest that the most common site of intraocular metastasis is uvea.

RECOMMENDATIONS

In the selection of corneas for transplantation from donors dying of malignancy the following recommendations are suggested

1. Absolute contraindication if malignancy is due to known viral etiology, blood and lymphatic system. Chemotherapy or radiation within 1 month of death.

2. Enucleation must be the procedure of choice in eye donors where the cause of death is cancer
3. After cutting the optic nerve look for any visible abnormality in the nerve such as thickness and grittiness of the nerve.
4. Eyes with macroscopic tumour masses should be rejected.
5. Cornea, iris and the anterior chamber of the eyes should be carefully evaluated on slit lamp to look for any gross tumour infiltrates or suspicious lesions such as patchy depigmentation
6. Vascularized cornea with or without scarring should be avoided as these have higher chances of having tumour seedings.
7. The corneoscleral button may be preserved in optisol and the rest of the eye ball subjected to histopathological examination.
8. If the cornea is used for transplantation, the corneoscleral rim must be subjected to histopathological examination and the recipient should be followed up for atleast 2 years.
9 Do not use the corneas in children or for keratolimbal grafts.

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This Paper was judged as the **BEST PAPER** of **CORNEA II** Session.

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An Innovative Technique Of Graft Preparation In PUK Using A Novel "Prick & Print" Technique

Dr. Sunandini Bose, Dr. Gautam Singh Parmar, Dr. Ashok Kumar Meena, Dr. Sachin Arya

INTRODUCTION

Peripheral ulcerative keratitis (PUK) is usually characterized by crescent shaped destructive inflammation of the juxtalimbal corneal stroma which is associated with an epithelial defect, presence of stromal inflammatory cells, and progressive stromal degradation and thinning.[1] PUK is often contiguous with adjacent conjunctival,episcleral, and scleral inflammation. The presence of such adjacent tissue inflammation aggravates the course of PUK and causes potentially serious complications, such as perforation of the cornea.[2-4]

Local and systemic autoimmune diseases are the various etiologies to be considered and thus immunosuppressive therapy is the mainstay

of treatment along with antibiotics, cycloplegic and lubricating agents. If not controlled with medical therapy, complications occurs despite the same surgical procedures may be required in the form of conjunctival resection, cyanoacrylate glue or more invasive procedures such as lamellar or penetrating keratoplasties.[5-10]

Irregular shape and peripheral location of such lesion pose a big challenge for ophthalmic surgeons to perform the keratoplasties in such patients. The keratoplasty options for these lesions are round or shaped grafts. The round grafts are may be eccentric and thus prone for rejection and sutures may involve optical center result in high astigmatism. To avoid visual axis suture related complications, large diameter round graft can be applied which are again prone for rejection and secondary glaucoma. There have been studies showing various round, biconvex or crescentic graft with promising results in various peripheral corneal diseases.[9-11]

So the choice of keratoplasty procedure for such lesions is eccentric shaped corneal grafts.

In this study, we report a novel "print & prick" technique to facilitate preparation of corneal graft in perforated peripheral ulcerative keratitis.

METHODOLOGY

A retrospective chart review of 15 eyes of 13 patients with perforated or non-healing PUK due to any reason, who underwent a penetrating or lamellar crescentic shaped graft, was done.A minimum follow up of 3 months post keratoplastywere only included.

Patients' demographic data were collected. Primary outcome measures were intra operative complications, graft apposition and tectonic integrity. Secondary outcome measures were visual acuity and postoperative complications.

Preoperatively, complete blood count, Mantoux test, chest X-ray, renal function test, RA factor, HbsAG, C reactive protein, sputum examination were done. Hepatic evaluation (r/o toxicity was done in subsequent follow-up visits to rule out toxicity with immunosuppressive therapy.

Patients were started on systemic immunosuppression, topical antibiotic, topical lubricants, systemic doxycycline

Preoperative evaluation and postoperative evaluation were done by a single observer (GSP).

Surgical technique

The novel "Prick and Print" technique was performed in all cases,which is a stencilling based technique in which we first performed peritomy adjacent to PUK followed by cauterisation of bleeding vessels. The outline of ulcer was marked using ink. A sterile transparent sheet of plastic from any source (drapes, suture wrappers etc.) was placed over ulcer and pricked with 26G needle along the ink marking. The sheet allowed to dry and placed over dried donor button mounted on artificial anterior chamber. The ink was applied along the pricking and imprint of the shape was made on the donor button. The donor was cut along the printed outlines partially with 15 degree lance knife and then cut full thickness with curved Vanna's scissors. The diseased host tissue was excised along the marking and the graft was then secured to the host with interrupted 10-0 nylon sutures.

Postoperative regime of patients comprised of topical moxifloxacin 0.5%, topical prednisolone 1%, topical lubricants, topical cycloplegics, oral immunosuppressive and oral doxycycline.

RESULTS

15 eyes of 13 patients underwent shaped corneal graft.The mean age of the patients was 40.61±19.44 years. The male: female ratio was 9:4. The mean follow up was 10.07 months. All surgeries were performed by a single surgeon (GSP). The demographic details, indication of surgery, graft details, results and complications are summarized in Table 1 & 2

Table 1

Eye number	SEX	AGE	PEROP BCVA	POSTOP BCVA	FOLLOW UP(M)
1	30	F	0.6	0.2	5
2	75	M	2.20	2.2	3
3	50	f	1.9	0.5	25
4	43	m	0.5	1	12
5	20	m	1.5	0.8	3
6	17	m	1.1	1.9	22
7	58	f	1	0.5	3
8	58	f	1.9	0.8	
9	27	m	0	0	3
10	12	m	1.7	0.8	3
11	62	m	1	1.5	3
12	36	m	0.2	1.5	18
13	60	f	1.9	0.3	24
14	60	f	1.5	0.6	
15	38	m	1.7	1	7

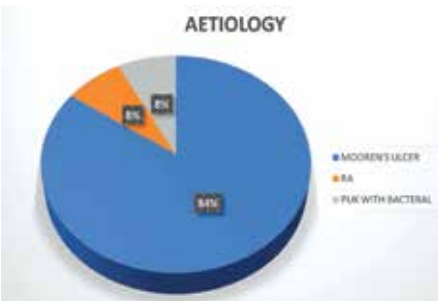
Table 2

eye number	INDICATION OF Sx	GRAFT SIZE	COMPLICATIONS	TOPOGRAPHY
1	puk	3 *4 mm		
2	puk	6.2*3mm		
3	puk	9.5 *4.5mm	Developed post operative glaucoma	
4	puk	11*3mm	Developed imsc	
5	puk	11.5 *5 mm	Developed Cataract	
6	puk	8*1.5mm	graft failure(after graft infiltrate), therapeutic pk done	
7	puk	10 *5mm		
8	puk	6*3mm		
9	puk	9 *5mm		
10	puk	12*3.5mm		
11	puk	10* 5mm	Same eye,other site puk	
12	puk	13*4mm	Developed corneal infiltrate adjacent to graft, patch graft done	K1-42.21d@158;K2-30.83@68
13	puk	5 *2mm		
14	puk	10*4mm		
15	puk	10*2.5mm		K1-45.9 @150;K2-39.9@60

11 (84.61%) patients were diagnosed with Mooren's ulcer due to no underlying evidence of any systemic or other ocular disease and the typical clinical characteristics.While 1 (7.69%) patient met with diagnostic criteria for rheumatic arthritis, 1 (7.69%) met with diagnostic criteria for peripheral corneal ulcer with bacterial involvement.

All the eyes presented with perforation of varying sizes. 2 patients underwent conjunctival resection before corneal grafting. While one eye underwent lamellar keratoplasty, 14 eyes underwent penetrating keratoplasty

Chart 1



Intraoperatively there was no overriding or shortening of any graft. All sutures were of equal length and depth. There was good graft host junction apposition. Tissue gaping or flattening were not noticed.

Postoperatively anatomical integrity, limbal architecture

and corneal contour were well maintained in all the grafts. All eyes had well-formed anterior chamber with no leak from any graft host junction (figure 1) with excellent postoperative results.

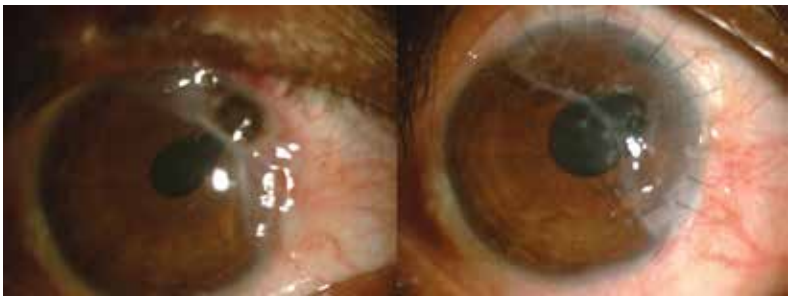
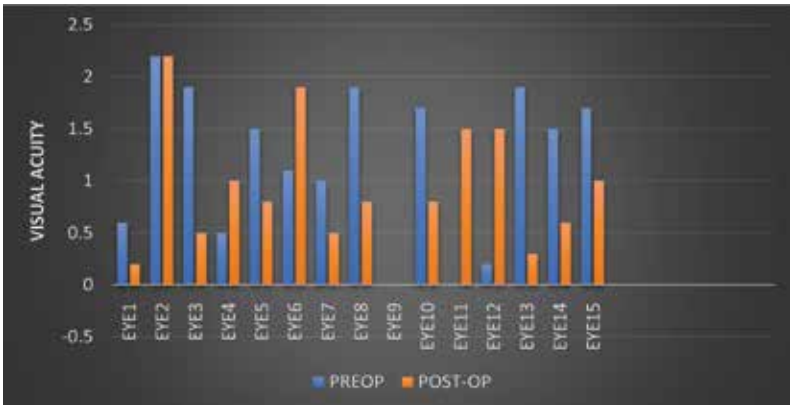


Fig. 1: Pre and post operative 6 months apart; showing good maintained corneal contour, limbalarchitecture, formed anterior chamber

Postoperative vision was variable. Nine eyes experienced improved BCVA postoperatively, while four eyes experienced worsening of BCVA and two eyes BCVA remained unchanged. (eye number 2 & 9) (Chart 2,3)

CHART 2

CHART 3 (pre & postoperative BCVA)



The mean BCVA changed from 1.18 Log Mar preoperatively to 0.93 Log Mar post operatively ($p<0.34$).

Four patients developed complications.One patient experienced diminished vision due to development of cataract (eye number 4). One patient developed PUK at other site in the same eye even with medical therapy (eye number 11). One patient developed graft infiltrate for which a patch graft was performed, but patient developed graft infiltrate again for which a repeat therapeutic penetrating keratoplasty was performed (eye number 6). One patient developed corneal ulcer at a site adjacent to the graft for which a patch graft was performed but graft melting developed for which a repeat therapeutic penetrating keratoplasty was performed (eye number 12).

DISCUSSION

Peripheral ulcerative keratitis presents with excessive tissue necrosis and involvement of the corneal limbus. Although interventional therapies with tissue adhesives as cyanoacrylate glue, conjunctival resection and amniotic membrane transplantation with systemic immunosuppression have been shown to have promising results, once perforation is present with excessive tissue necrosis tectonic keratoplasty either penetrating or lamellar appears to be the best option.

Being a tertiary eye care center most of the patients that presented in our institute were on topical antibiotics and topical corticosteroids, despite this a significant number presented with perforated or impending perforation.

Although tissue adhesive can be performed in small perforation, proper sticking and tectonic stability is of great challenge in these peripheral perforations.

While a large diameter eccentric corneal graft can provide good tectonic support there are chances of sutures coming into pupillary/ visual axis and more chances of graft rejection due to more area covered with grafted tissue. Small diameter round grafts have been shown to have promising results emphasizing the advantages of over large grafts, which include lower risk of graft rejection, peripheral anterior synechiae formation and secondary glaucoma, and good visual acuity despite graft failure because of eccentric location and noninvolvement of the pupillary area.[11-12] When there is extensive or more clock hour involvement of limbus, a small diameter round eccentric graft will be insufficient to cover the required limbal involvement without sutures coming into the visual axis.

In such cases a customized shaped corneal graft can be beneficial to spare as far as optical axis as possible and at same time involve more limbal clock hours in grafting.

As our primary goal was not to report better visual outcome than other techniques that have already been described but to describe a surgical technique that appears to be simpler to perform than already described technique and has good repeatability.

In previous studies by Parmar Pet al[10] both biconvex and crescentic graft have been performed for various disease entities. There has been use of corneal trephine to mark the corneal arc of host tissue and limbal arc was cut freehand. Also the donor tissue was cut in similar pattern with the limbal arc cut freehand after securing the graft at the host tissue limbus with two interrupted sutures. Cheng et al,[13] in the management for severe astigmatism for peripheral corneal degeneration did a lamellar keratoplasty, while the donor tissue dissection was done using four corneal trephine to mark out the exact size and shape. Two corneal trephines 9 mm and 14 mm were used to mark the inner and outer diameter while two trephines 2-3 mm were used to mark the ends of arc.

Not only the use of multiple trephines has higher cost per case, but also the free hand dissection of the donor tissue can lead to graft host disparity and cause malapposition. In our technique the use of minimal instruments and only plastic drape makes it cost effective as well as can be performed by any beginner surgeon without the use of much surgical instruments or technical issues.

An eccentric crescentic corneal graft with the proposed technique not only ensures the limited proximity to the central optical axis but also rest of the cornea. Optical axis remains clear in case of graft failure ensuring good BCVA. Secondly, marking the exact ulcer on a surface helps in making out the exact shape and size of graft without causing any disparity. Thirdly, as the technique is similar for all cases of varying sizes and shapes, repeatability is good even with a lamellar keratoplasty. Even inexperienced surgeon can perform the technique with ease. Despite the marked central asymmetry caused by the eccentric graft in some cases, the surface of the central cornea may be relatively regular, allowing acceptable visual outcome.

In our study, 9 patients improved in BCVA, while 4 worsened. While two patients suffered from graft infiltrate and infiltrate adjacent to graft, one patient (eye number 12) maintained a BCVA of 20/20 prior to developing infiltrate for one year post keratoplasty. One patient developed cataract and was satisfied with the tectonic effect of penetrating keratoplasty, but refused cataract surgery with IOL implantation. 2 eyes maintained the same BCVA, in which one patient had cataract in the eye preoperatively and refused a cataract extraction with IOL implantation.

Limitations of our study are small follow up and unavailability of corneal topography in some patients.

CONCLUSION

This novel technique is simple & has good reproducibility in preparing a graft in PUK. It also provides optimum tectonic stability

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This Paper was conferred with the **BEST PAPER** of **AIOS-CORNEA AWARD.** This paper was also judged as the **BEST PAPER** of **CORNEA III** Session.

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Simplifying Descemet's Membrane Endothelial Keratoplasty (DMEK)

Dr. K.S. Siddharthan

INTRODUCTION

Worldwide there is an increasing adoption of Descemet Membrane Endothelial Keratoplasty (DMEK) representing a major shift in the treatment paradigm for Fuchs' endothelial dystrophy and other forms of Endothelial Dysfunction. Studies on DMEK have demonstrated better visual outcomes, faster visual rehabilitation, and a significantly

lower incidence of rejection compared with its predecessors, Descemet stripping endothelial keratoplasty (DSEK) and Penetrating keratoplasty. Despite these advantages most of the corneal surgeons in India have been slow to adopt DMEK, in part because DSEK still remains an excellent procedure, but also owing to what has been described as the steep learning curve of DMEK.

METHODS

Three key challenges for the DMEK surgeon are 1. Stripping the donor DM, 2. Transferring & Handling the fragile Descemet's membrane and 3. Placement and proper Orientation of the graft in the anterior chamber. During stripping the donor DM, a small tear can cause wastage of the tissue. The problem does not end there. Once the DM is stripped it characteristically scrolls with the endothelial side out configuration, thus making it unsafe to handle the tissue. Further, the dark pigmented brown eyes in Indian patients gives less contrast while in the anterior chamber when compared with non-pigmented western eyes. Adding to the difficulty is that the tissue orientation is not easily visualized through hazy diseased corneas. For all of these reasons, discerning the correct orientation of a DMEK graft in the anterior chamber can be a challenge, and accidental placement of upside-down grafts remains a cause of iatrogenic primary graft failure in DMEK even in the hands of experienced DSEK surgeons. A number of groups worldwide have developed orientation techniques, including the use of various external light sources, intra-cameral instrumentation of the graft scroll, and modifications to the graft itself.

RESULTS

We initially started doing DMEK in 2013. 47 patients completed 1 year follow-up. Even though the best corrected visual acuity drastically improved in all the cases, what was worrying us was the percentage of Endothelial Cell Loss (ECL) and the Failure and Complication rate. The Mean ECL at 6 months and 1 year were 24% and 31% respectively. The Complication rate was 28% and the Successful Outcome was 83% in this group. This unpredictable outcome after DMEK, is the main reason why not even a few corneal surgeons in India are venturing into this technique.

OUR TECHNIQUE TO SIMPLIFY DMEK

We thought it necessary to improvise this technique and address these limitations. We developed and validated three novel methods.

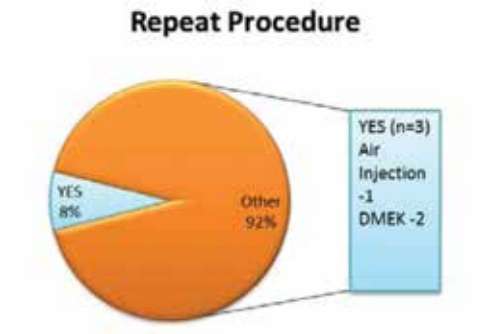
1. Single Pull technique for donor DM removal 2. Prototype DM Injector 3. Stromal-sided L-stamp. These three unique innovations by us provides definitive and intuitive technique to strip, transfer and orient the DM intra operatively before elevating the DM with air bubble inside the anterior chamber.

Further after improvising the technique we performed DMEK in 40 eyes of 39 patients. These patients were followed up to 6 months and the results are as follows:

SUMMARY OF RESULTS WITH OUR IMPROVISED TECHNIQUE FOR DMEK

Data Summary				
Age	65+/-11.5	Male	65+/-12.1	
		Female	66+/- 9.1	p>0.05
Gender				
Male			82%	
Female			18%	
Indication				
PBK			68%	
BK			10%	
ABK			3%	
Fuch's			20%	
Mean LOG MARG Visual Acuity				
PRE OP			1.257+/0.441	p<0.001
POST OP			0.265+/0.398	
Lines Improved				
Nil			8%	
1 - 3			13%	
4 - 6			60%	
> 6			20%	
Mean ECD				
PRE OP			2191+/-292	p<0.001
POST OP			1854+/-294	
ECD Difference			328+/-36	
Loss %			15.1%	

Complication	
YES	5%
NO	95%
Repeat Procedure	
YES	8%
NO	92%
OUT COME	
SUCCESS	92%
FAILURE	8%



DISCUSSION

Endothelial cell loss at 6-month follow-up period was 27.9 ± 16.0% after DMEK in Terry MA et al study. Theofilas and associates reported an endothelial cell loss of 41% in the DMEK group at 6 month post-operative period. Endothelial cell loss was 32% ± 20% after DMEK in 38 eyes that reached the 6 month examination in Price et al study. Recently in 2015 Gorovoy et al reported an endothelial cell loss of 19% at 1 year follow up.

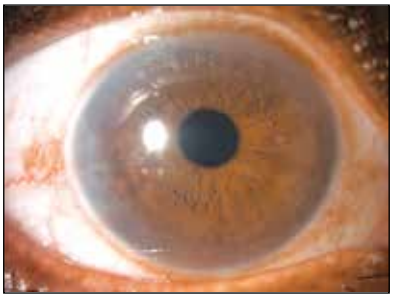
Our modified technique, has shown the least endothelial cell loss and failure rates compared to the above studies, thus simplifying the procedure and stressing the importance of a making a standardized protocol to achieve a favourable outcome so that many corneal surgeons in India can confidently start DMEK .

CONCLUSION

DMEK will definitely be the procedure of choice for endothelial diseases in future and it is high time we adopt standard and simple techniques to increase the success of DMEK.

PICTURES

Fuch's Endothelial Dystrophy



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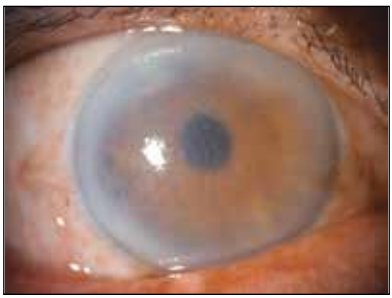
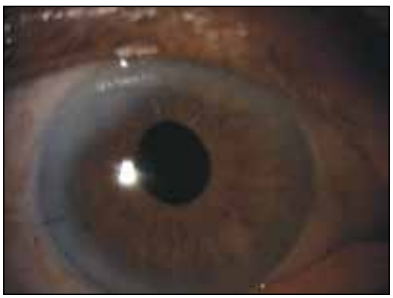
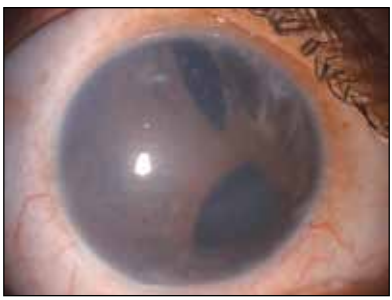


Pseudophakic Bullous Keratopathy



Post DMEK



Iridocorneal Endothelial Dystrophy (ICE)

Post DMEK

This Paper was conferred with the **AIOS-REMA MOHAN AWARD** for the **BEST PAPER** of **DIABETIC RETINOPATHY & MEDICAL RETINA** Session. This paper was also judged as the **BEST PAPER** of **DIABETIC RETINOPATHY & MEDICAL RETINA I** Session.

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Diabetic Macular Edema Or Masquerade?

Dr. Ashish Khodifad, Dr. Nagesha

INTRODUCTION

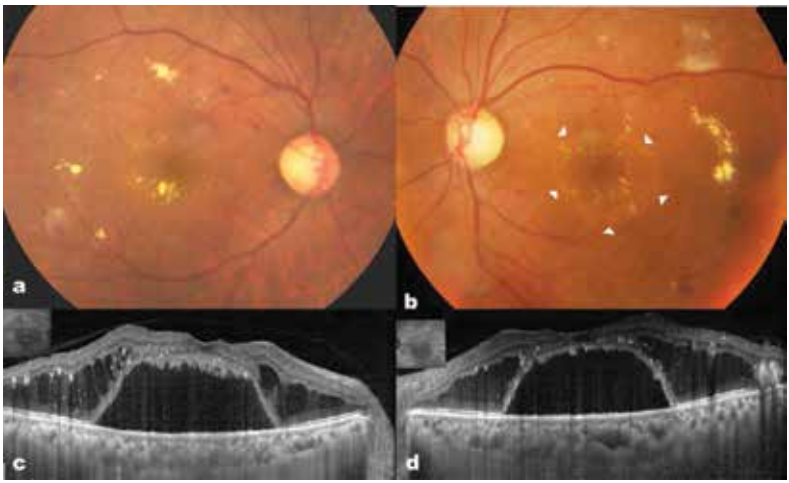
Paraproteinemia is the presence of excess amount of single monoclonal gamma globulin in the body. This results secondary to multiple myeloma, immunocytoma or Waldenstrom macroglobulinemia.[1] They are characterized by signs and symptoms of hyper viscosity and hemorrhagic tendency. Ocular manifestations have been described which are characterized by retinal venous occlusions, optic disc swelling, and rarely serous macular detachments.[2-5] In the absence of systemic symptoms, ocular manifestations alone may pose diagnostic and therapeutic challenge. Moreover in the setting of background diabetic retinopathy, signs of fundus changes of paraproteinemia are overlooked and managed in the line of standard diabetic retinopathy treatment.

In such situations, unresponsive cases need prompt further evaluation to rule out comorbid conditions which not only unearth serious underlying secondary conditions but also help in correct management of such cases. Here, we have encountered similar cases of serous maculopathy masquerading as nonresponsive diabetic macular edema in otherwise systemically asymptomatic patients. Presence of paraproteinemia was discovered in all these cases on the basis of systemic evaluation prompted by loss of vision and nonresponse to standard treatment.

CASE 1

A 47 year old man with a medical history of diabetes mellitus and moderate non proliferative diabetic retinopathy (NPDR) was on regular follow up since 5 years. Best corrected visual acuity (BCVA) was $20/20^{(p)}$ in both eyes and retinopathy appeared stable at all the visits and same is his glycemic control (HbA1c Range 5-6). Recently,

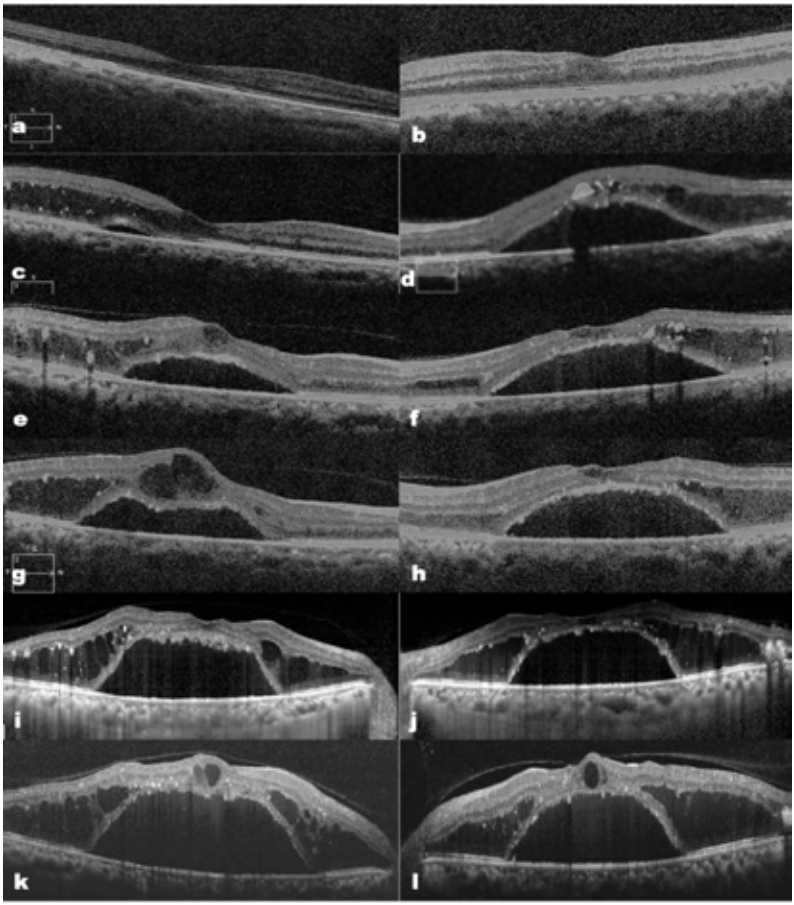
he walked into clinic with recent complaint of defective vision in left eye. BCVA was 20/20(P) in right eye and 20/30 in left eye. Dilated fundus examination showed features of moderate NPDR and macula showed near circular 2-3 disc diameter size neurosensory detachment with yellowish precipitates underneath (Picture 1a,b). The venules appeared slightly wider with AV ratio of 1:4. Optical Coherence Tomography (OCT) scan through macula showed foveal detachment with intraretinal cystoid edema in the parafoveal region (Picture 1c, d). Fundus fluorescein angiography (FFA) showed no significant leakage which could account for the macular changes.



Pic. 1: Case-1, showing background diabetic retinopathy with bilateral serous detachment (arrow heads) of the macula (a, b). Corresponding OCT picture showing large foveal detachment with surrounding outer retinal cystoid edema (c, d). (Insets show level of macular scans).

In the background of diabetic retinopathy, diagnosis of centre-involving macular edema was made and intravitreal antiVEGF was tried. Multiple antiVEGF injections followed by trial of intravitreal steroids failed to resolve the macular edema. His visual acuity dropped to 20/40(P) in right eye and 20/60 in left eye.

Throughout the follow-up visits, patient's history was unremarkable except for blurred vision. He denied any systemic illness other than diabetes. Slight engorged venules and progressive worsening of foveal detachments (picture 2) prompted us to investigate for hyper viscosity conditions. Serum electrophoresis showed presence of M band and bone marrow aspiration showed 30% marrow cellularity with



Pic. 2: Case-1 with series of OCT scans (c-i) through macula over 12 months showing progressive increase in foveal detachment and outer retinal cystoid separations. (a, b are scans 2 years before the onset of symptoms showing near normal macular configuration)

predominantly mature and few immature plasma cells; suggestive of multiple myeloma. Patient was referred to hematologist for further systemic evaluation. He later was started with Immunosuppressive therapy (Tab Rituximab) and subsequent follow-ups showed resolution of hyperviscosity and stabilization of maculopathy.

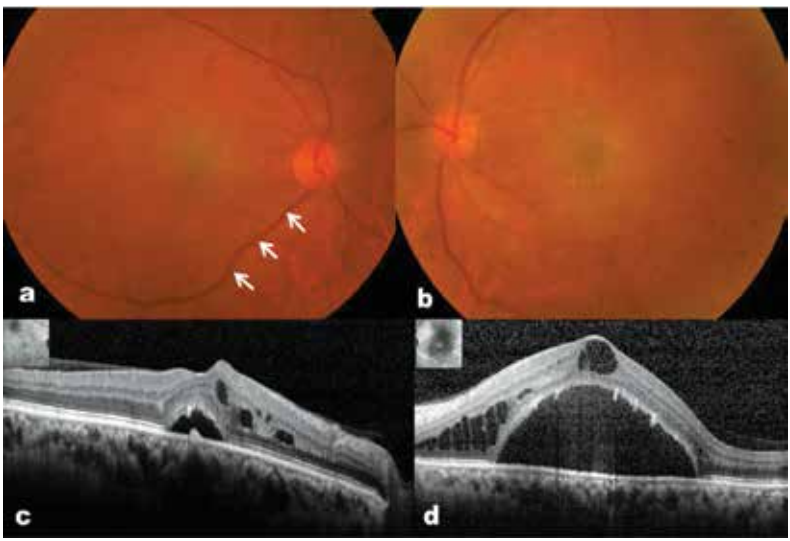
CASE 2

A 63 year old man with a medical history of diabetes mellitus for 20 years presented with complaint of defective vision in left eye since

5 months. BCVA was 20/30$^{(P)}$ in right eye and 20/120 in left eye. Slit lamp evaluation showed lens changes in both eyes. Dilated fundus examination of right eye showed few dot blot hemorrhages and dull foveal reflex. Left eye showed dot blot hemorrhages in 2-3 quadrants and the macula showed 2-3 disc diameter size neurosensory detachment with subretinal yellowish precipitates.

FFA showed moderate NPDR changes with no significant leakage at macula. OCT scan through macula showed foveal detachment in left eye and small pocket of subretinal fluid in right eye. Patient was treated as center involving macular edema. Macular changes remained unchanged after 2 monthly injections of AntiVEGF.

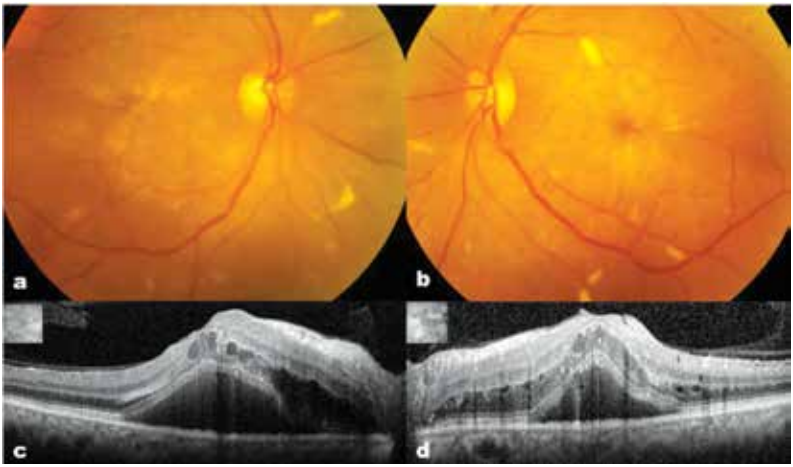
On follow up, retinal veins appeared more dilated in both eyes without tortuosity or increase in hemorrhages.Hyperviscosity syndrome was suspected and was subjected to further systemic work-up. Serum immunoglobulin IgM was >5000 µg/dl and electrophoresis showed presence of 'M' band. Diagnosis of Waldenstrom macroglobulinemia was made and started on systemic Brotezomib followed by Rituximab. On subsequent visit, right eye showed resolution of macular edema and left eye showed slight decrease in height of foveal detachment.



Pic. 3: Case-2 fundus showing appearance of engorged retinal venules (arrows) in both eyes over background diabetic retinopathy changes (a, b). OCT pictures (c, d) showing asymmetrical foveal detachment with intraretinal cystoid edema which received multiple anti-VEGF injections. (Insets show level of macular scans).

Case-3

A 48 year old female with 15 years of diabetes history presented with complaints of blurred vision in both eyes since last 1 month. She had history of weight loss of more than 20 kg in the last 1 year.She has taken treatment for kidney stones. The BCVA was 20/60 in both eyes and anterior segment of the right eye showed few pigments on lens capsule suggestive of old anterior uveitis. Fundus examination showed background diabetic retinopathy with peripapillary retinal edema and serous detachment at macula. (Picture 4)



Pic. 4: Case-3 fundus shows background diabetic retinopathy with central serous detachment of macula (a, b). Corresponding OCT pictures confirming serous detachment with intraretinal cystic changes (c, d). (Insets show level of macular scans).

Further systemic evaluation was carried out as the maculopathy did not respond to multiple intravitreal avastin and steroids. Blood examination revealed anemia of 9.2 mg%, and serum protein estimation revealed abnormal globulin levels and electrophoresis confirmed presence of M band. A diagnosis of Waldenstrom macroglobulinemia was made and referred to oncologist for further evaluation and management

DISCUSSION

Serum hyperviscosity is the etiologic factor in several ophthalmic disorders, many of which may have similar retinal findings. The above 3 cases present significant diagnostic and therapeutic challenge. Here, patients with history of background diabetic retinopathy would lead examiner to probable diagnosis of diabetic macular edema. In

the absence of other associated fundus features as in case 1 along with denial of any systemic symptoms delayed early recognition of paraproteinemic maculopathy.

In the second case, the engorged veins developed 4-5 months after development of maculopathy which otherwise mimicked diabetic macular edema, especially in left eye. The serous detachments in these cases are thought to be exudative in nature; and found to have IgM in subretinal space suggesting that an increased osmotic gradient causes fluid accumulation under the retina.[6] Ashton and Foos et al[7] observed that hyperviscosity can cause stasis and hypoxia leading to endothelial decompensation. This causes secondary breakdown of blood retinal barrier in addition to RPE decompensation. Coexisting diabetic retinopathy exacerbates the severity posing additional risk factor enhancing leakage and so the poor treatment response.

Wide spectrum of ocular manifestations has been described in diagnosed case of gammaglobulinopathy. They include venous stasis retinopathy, immunoprotein deposition in the cornea, IgM deposits in retinal layers and serous macular detachment. All these are secondary to serum hyperviscosity and clinical recognition of these findings is early when the systemic history is known. On the other hand, diabetic retinopathy secondary to poorly controlled diabetes can present with engorged veins,retinal hemorrhages, venous occlusion and also serous macular detachment. The overlap of fundus findings may delay the recognition of early fundus features of paraproteinemias.

Angiographically silent macular detachment is the hallmark of immunogammapathy associated macular detachment.[8] On the other hand, differentials like central serous chorioretinopathy, hypertensive retinopathy, inflammatory choroidopathy like lupus and infiltrative lesions like lymphoma invariably present with some angiographic leakage at the level of RPE and/or retinal vasculature. In all the above cases, FFA showed minimal leakage which could not be accountable for amount of macular edema and foveal detachment which could clue us to investigate for exudative conditions.

The paraproteinemic maculopathy becomes symptomatic when IgM level exceeds 4000 mg/dl in diabetics and 7000 mg/dl in non-diabetics and serum viscosity exceeds 5.5cP.[9] This is the probable reason that ocular manifestations preceded the systemic symptoms in our patient who was a known diabetic for more than 5 years. Early recognition of this entity and prompt referral to hematologist is necessary for

systemic monitoring and treatment. Immunosuppressives and/or plasmapheresis are indicated in cases of maculopathy secondary to hyperviscosity. In present case series, chemotherapy resulted in slight decrease in macular edema though visual acuity remained the same. Various intravitreal injections[9] failed to show a definitive benefit in such cases as mirrored in our cases. Majority of cases will have persistent subretinal fluid despite improvement of systemic hyperviscosity and so bad visual prognosis.

To conclude, diagnosis of paraproteinemic maculopathy mimicking as recalcitrant diabetic macular edema in otherwise systemically asymptomatic patients poses a diagnostic challenge. Though rare, prompt recognition of this entity amidst plethora of differentials is very important as underlying conditions carry high risk of morbidity and mortality. A thorough evaluation by a hematologist or an oncologist should be carried for early recognition and prompt treatment.

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This Paper was judged as the **BEST PAPER** of **DIABETIC RETINOPATHY & MEDICAL RETINA II** Session.

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Correlation Of OCT Angiography (OCTA) Features Of IPCV With ICG Angiography (ICGA)

Dr. Rakesh Juneja, Dr. Navneet Mehrotra, Dr. Manish Nagpal

ABSTRACT

AIM

To correlate angiographic findings of IPCV (Idiopathic Polypoidal Choroidal Vasculopathy) on ICGA with morphological features on OCTA, pre and post treatment

SETTINGS AND DESIGN

Single-center, prospective, observational study

METHODS AND MATERIAL

20 eyes of 20 patients, treated with focal laser and anti-VEGF, underwent baseline OCTA and ICGA. All cases were followed up at 1, 3 & 6 months

STATISTICAL ANALYSIS USED

Descriptive analysis

RESULTS

ICGA detected polyps in 20 and BVNs in 17 eyes. OCTA detected each in 14 eyes. Pre treatment, BVN appeared as hyper-flow lesion, polyp as hyper-flow round structure surrounded by a hypo-intense halo corresponding to the hyperfluorescence area, surrounded by hypo fluorescence halo and a hyperfluorescent 'hot spot' on ICGA. Post treatment revealed decrease in size and number that corresponded

to reduced hypofluorescence halo and hyperfluorescent 'hot spot' on ICGA

CONCLUSION

OCTA as a non-invasive tool correlates accurately with ICGA findings for assessing the polyps and BVNs in IPCV and it can be used as an alternative diagnostic test

KEYWORDS

Idiopathic polypoidal choroidal vasculopathy, optical coherence tomography angiography, indocyanine green angiography, branch vascular networks, polypoidal lesions

KEY MESSAGES

OCTA is a promising "non-invasive" tool that can be used as an "alternative" diagnostic test and is certainly the 'future of IPCV imaging'

INTRODUCTION

IPCV is an acquired, abnormal choroidalvasculopathy.[1,2] IPCV is characterized by polypoidal dilations and choroidal branching vascular networks observed on ICGA.[1,2,3,4] OCT shows polypoidal dilations, which are characterized by dome like elevations of retinal pigment epithelium.[5,6,7] Branching vascular networks appear as 'double layer sign'.[8]

OCTA works on the principle of 'decorrelation' and generates 3 D maps of microvasculature flow pattern from retinal capillary plexus to choroidal vasculature.[9,10]

With the objectives, to assess IPCV features on OCTA and to correlate with ICGA pre and post treatment, a prospective study was conducted, among Indian subset of population, in a tertiary care clinical setting.

SUBJECTS AND METHODS

STUDY DESIGN AND PATIENT ENROLMENT

This was a single-center, prospective, observational study with data collected from patients with IPCV diagnosed on OCT and ICGA and underwent OCTA examination at baseline and subsequent follow-ups. All cases that were enrolled provided informed consent to be enrolled in study. The synopsis was reviewed and approved by the Ethical Committee. Patients recruited through the retina clinic from

July 2016 to August 2017, were enrolled in the study, and were assigned a registration number, and no patient identifiable information was collected. The study adhered to the tenets of the Declaration of Helsinki.

ELIGIBILITY CRITERIA AND DATA COLLECTION

Data was collected under the following headings: demographic details, history of presenting illness, eye laterality, history and duration of diabetes, hypertension or any other associated systemic comorbidities, diagnosis of retinal pathology, clinical examination details including visual acuity at presentation and follow-up with imaging (color fundus photography, OCT, OCTA, FA and ICGA), treatment details, complications (if any) and treatment given for that complication. Inclusion criteria were: (1) Cases diagnosed as IPCV on the basis of ICGA and OCT features who underwent OCTA imaging (2) complete availability of documentation till the last follow-up. If any one of the above mentioned inclusion criteria was not met, patients were excluded from the study.

Data analysis and statistical methods

Various features of IPCV cases at baseline and all follow-ups during the course of study were tabulated and computed using descriptive statistics.

RESULTS

Baseline Demographics

Thirty-two eyes of 32 patients diagnosed as IPCV were studied. Out of which, 20 eyes of 20 patients who met our inclusion criteria were included in the study and rest were excluded. The average age of patients in our study group was 54-76 years. Fourteen patients were males and 6 patients were females. All eyes had unilateral presentation. Hypertension was the major comorbid condition comprising 14 cases (Table 1).

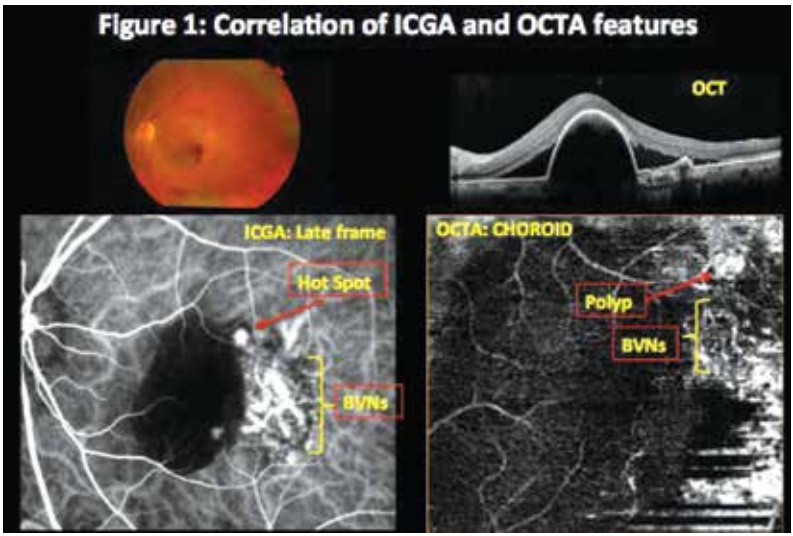
Table 1: Baseline Demographics

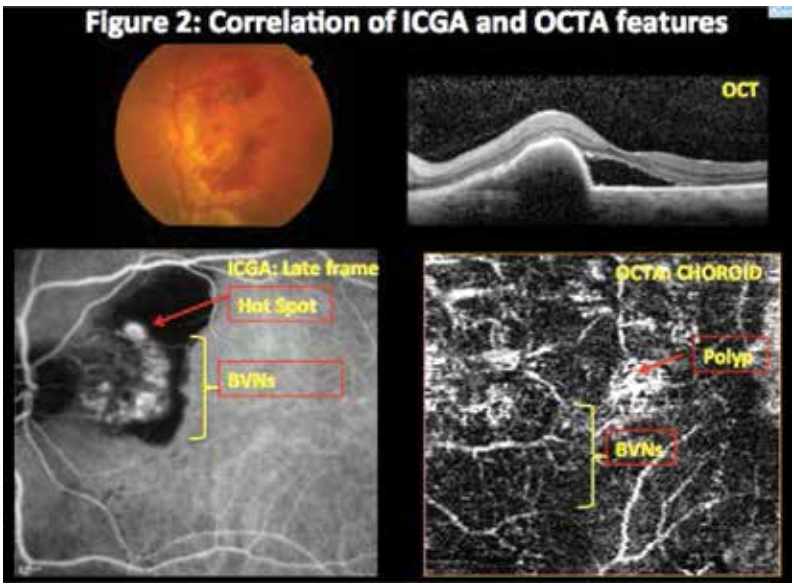
PARAMETERS	n (%)
No. of patients	20
No. of eyes	20
Female	14(70%)
Male	6(30%)
Age (mean)	65
Age (Range)	54-76
Unilateral	20(100%)
Bilateral	0
Hypertension	14

OCTA features of IPCV and its correlation with ICGA

ICGA detected polyps in 20 and branch vascular networks (BVNs) in 17 eyes. OCTA detected each in 14 eyes. Pre treatment, BVN appeared as hyper-flow lesion, polyp as hyper-flow round structure surrounded

by a hypo-intense halo corresponding to the hyperfluorescence area, surrounded by hypofluorescence halo and a hyperfluorescent 'hot spot' on ICGA. Post treatment revealed decrease in size and number that corresponded to reduced hypofluorescence halo and hyperfluorescent 'hot spot' on ICGA (Figure 1,2,3,4,5). At baseline, OCTA showed





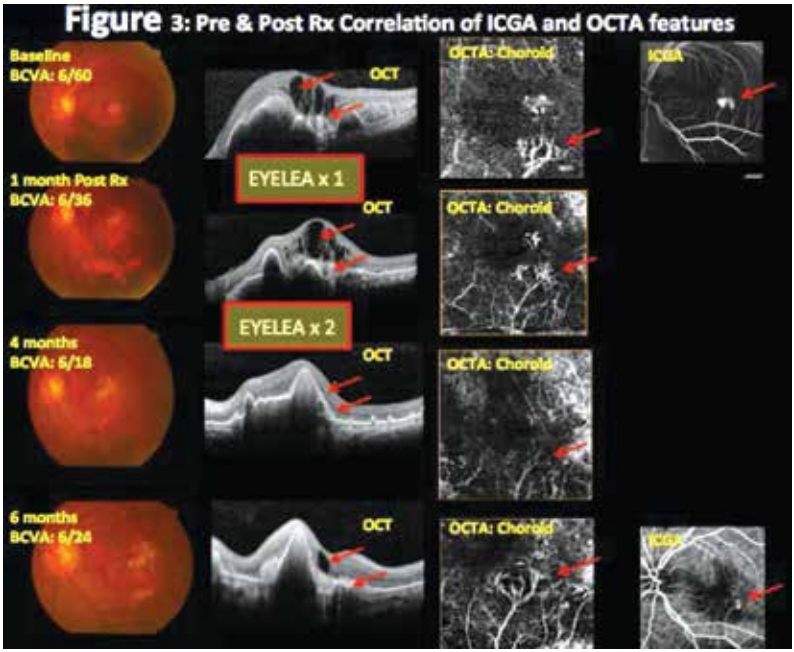
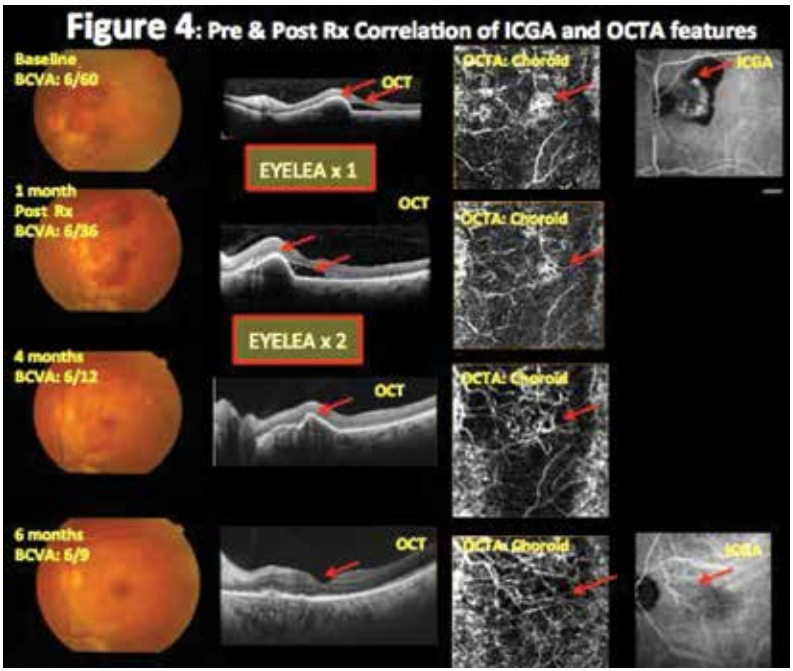


Figure 3: Pre & Post Rx Correlation of ICGA and OCTA features
Baseline
BCVA: 6/60
OCT
OCTA: Choroid
ICGA
EYELEA x 1
1 month Post Rx
BCVA: 6/36
OCT
OCTA: Choroid
EYELEA x 2
4 months
BCVA: 6/18
OCT
OCTA: Choroid
6 months
BCVA: 6/24
OCT
OCTA: Choroid
ICGA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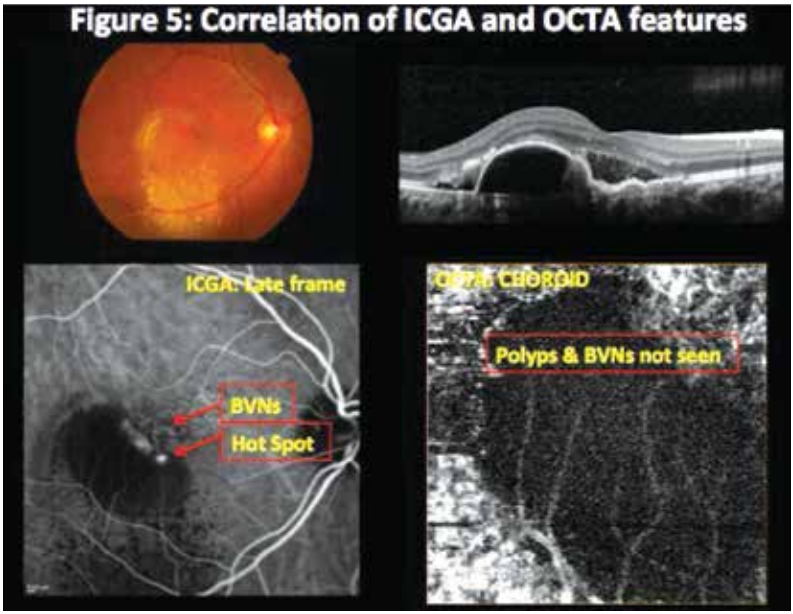
1 month
Post Rx
BCVA: 6/36
OCT
OCTA: Choroid
EYELEA x 2
4 months
BCVA: 6/12
OCT
OCTA: Choroid
6 months
BCVA: 6/9
OCT
OCTA: Choroid
ICGA



70% sensitivity as compared to ICGA in detecting IPCV (Table 2) whereas during all follow-ups post treatment OCTA revealed 100% sensitivity as compared to ICGA. (Table 3)

Table 2. Comparison of sensitivity between OCTA and ICGA to screen IPCV at baseline

TOOL	PROPERTY	No. of IPCV cases (at Baseline)	No. of patients diagnosed (at baseline)	Sensitivity to screen at baseline
ICGA	INVASIVE	20	20	100%
OCTA	NON INVASIVE	20	14	70%

Table 3. Comparison of sensitivity between OCTA and ICGA to screen IPCV at Follow-ups

TOOL	PROPERTY	No. of IPCV cases (at Follow-up)	No. of patients diagnosed (at Follow-up)	Sensitivity to screen at Follow-up
ICGA	INVASIVE	6	6	100%
OCTA	NON INVASIVE	6	6	100%

DISCUSSION

Polypoidal lesions in IPCV characteristically appear as hyper-flow round structures on OCTA. However, in certain cases, hypo-flow structures are also observed. This absence of signal does not mean that there is no blood flow; rather, it indicates that blood flow is not within the detection limit of the OCTA device. This could be due to either increased or decreased flow in the polyps and subsequent nonvisualization of the vascular structure. Although choroidal blood flow is known to be higher than retinal blood flow,[11] and some studies of IPCV hemodynamics have suggested that these lesions originate from choroidal vascularization,[12] this hypothesis is very unlikely. High blood flow in the polyps is theoretically possible, but ICGA has revealed that the polyps do not fill very rapidly during early-phase angiography. We hypothesize that the apparent absence of OCTA signal within polypoidal lesions could be due to either the presence of turbulent blood flow inside of the polyps – impeding the representation of this flow – or to the fact that blood circulates only at the periphery of the aneurysmal dilation. The last hypothesis is sustained by the fact that the pigmentary epithelium detachment associated with the polypoidal structure also demonstrates an attenuated OCTA signal.

OCTA allows for the visualization of retinal microvasculature by detecting intravascular linear blood flow,[13,14] and indeed, in our patients, the branching vascular network, which is characterized by linear blood flow, was clearly detected using the OCTA's priniciple of decorrelation.

In conclusion, the results of our study provide new insight to image IPCVs noninvasively. However, ICGA still stands as the age-old, time-tested, gold-standard modality for diagnosing IPCVs with 100% accuracy at both baseline as well as at all follow-ups. OCTA noninvasively does complement and correlates with ICGA in detecting IPCVs with a fairly good sensitivity of 70% at baseline and equivalent 100% sensitivity at all follow-ups.

OCTA is a noninvasive imaging modality, and we have demonstrated that it allows for the visualization of different structures in IPCV. The branching vascular networks are clearly and consistently visualized as hyper-flow lesions, but further improvements in OCTA knowledge are needed to gather information on the specificity of the different intensity characteristics of polypoidal lesions.

The major limitations of our study are the small sample size and lack of swept source OCTA. The major strength of the study is that it provides data on Indian subset of population, is only the second study in literature incorporating such a large number of IPCV cases and provides data both at baseline as well as on follow-ups.

OCTA thus is a promising noninvasive tool and correlates with the information provided by invasive ICGA and with further upcoming advances in bio-medical engineering it seems to be the future of imaging in IPCV.

ABBREVIATIONS

OCT optical coherence tomography

BVN branch vascular network

IPCV idiopathic polypoidal choroidal vasculopathy

OCTA optical coherence tomography angiography

ICGA indocyanine green angiography

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Understanding Molecular Signatures Driving Pain And Nociceptive Response In Evaporative Dry Eye

Dr. Kanchan Sainani, Dr. Rohit Shetty

INTRODUCTION

The prevalence of dry eye disease (DED) worldwide ranges from 5.5% to 33.7%.[1] Due to its high prevalence it is a public health concern with a significant economic burden. The hallmarks of DED include discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. In a subset of patients with DED the standard therapeutic strategies fail to alleviate the symptoms.[2,3]

Despite the knowledge available on the pathophysiological mechanisms of DED, there is a lack of substantial understanding with relevance to the etiopathology of the symptoms and their association with clinical findings. The source of ocular discomfort or pain in DED cannot solely be explained by tear film metrics suggesting the role of other factors in causation of symptoms. Pain associated with dry

eye has been described as neuropathic pain[4-6] and there have been emerging reports regarding dysfunctional ocular somatosensory nerves including the sub-basal nerve plexus in ocular pain.[7]

In the current study the association between the severity of dry eye symptoms (pain and/or discomfort), inflammatory markers in tears, corneal dendritic cell density, corneal sub-basal nerve plexus features, was determined.

PURPOSE

To determine the biological basis of pain and discomfort associated with evaporative dry eye (EDE).

MATERIALS AND METHODS

This is an observational case control clinical and clearance was taken from Institutional Review board and was cleared by the Ethics Committee and the study adhered to the "Declaration of Helsinki".

Study Population. A total of 60 patients who presented to our clinic with symptoms of Dry eyes due to evaporative dry eye disease were included in the evaporative dry eye (EDE) group and 33 healthy volunteer subjects constituted the control group. A thorough medical history was elicited to rule out any other ocular and systemic comorbidity, following which visual acuity, refraction, detailed slitlamp examination and fundus evaluation, and DED investigations were performed. All the tests were performed under ambient conditions of temperature and humidity. A hanging drop of 1% fluorescein stain from fluorescein strip (Conta Care Ophthalmics and Diagnostics, India) was instilled in the inferior cul-de-sac of the conjunctiva to measure the tear film break-up time (TBUT) in seconds (using a stopwatch) and corneal and conjunctival epithelial staining, if present. Schirmer's test without anaesthetic was performed using sterile Schirmer's strips—Whatmann filter paper (5 × 35 mm^2, Conta Care Ophthalmics and Diagnostics, India). Schirmer strips were placed in the lower conjunctival sac at the junction of the lateral and middle thirds of the lower eyelid, without instilling anaesthesia. All patients were seated at rest with their eyes closed. Meibomian gland status was examined using infrared meibography (Oculus, Wetzlar, Germany) and was scoring was performed based on the loss of meibomian glands for each eyelid. Patient's ocular pain or discomfort was graded using ocular surface disease index (OSDI) questionnaire and the total OSDI scores were further classified into discomfort and vision-related subscales. Patients

with OSDI scores indicating symptoms of dry eye, normal Schirmer's test values, and low TBUT were categorized as EDE. The control group included age matched healthy volunteers with Schirmer's test values > 10 mm and TBUT > 5 seconds and no symptoms of dry eye and other ocular conditions. Exclusion criteria included the use of contact lenses, the presence of drug allergy or ocular or systemic diseases with ocular manifestations such as Sjogren's syndrome, rheumatoid arthritis, and diabetes mellitus. Patients with disorders involving the lacrimal gland (congenital alacrimia, Steven-Johnson syndrome) and lid disorders including clinically evident meibomian gland dysfunction along with patients using topical medication were also excluded.

Tear samples were collected using Schirmer's strips by following Schirmer's test I protocol. Tear analytes were extracted from Schirmer's strips by cutting them into small pieces, agitation in sterile phosphate buffer solution (PBS) for 2 hours at 48 degree Celsius followed by centrifugation.

The levels of various inflammatory proteins in the tears were measured using cytometric bead array (BD CBA Human Soluble Protein Flex Set System, BD Biosciences, Haryana, India) on a flow cytometer (BD FACS Calibur, BD Biosciences). The CBA for this study was designed for simultaneous detection and quantification of interleukin (IL)-1a, IL-1b, IL-2, IL- 4, IL-6, IL-8, IL-9, IL-10, IL-12/IL-23p40, IL-12p70, IL-13, IL-17A, IL-17F, IL-21, neuropeptide-Y, chemokine ligand 2 (CCL2)/monocyte chemotactic protein (MCP)-1, C- X-C motif chemokine 10 (CXCL10)/IP-10, intercellular adhesion molecule 1 (ICAM1), interferon (IFN)- c, and vascular endothelial growth factor (VEGF).

In Vivo Confocal Microscopy (IVCM). IVCM imaging was performed using Rostock Corneal Module/Heidelberg Retina Tomographll (RCM/HRT ll, Heidelberg Engineering GmBH, Dossenheim, Germany. 0.5% proparacaine drops were used to anaesthetize the cornea prior to the procedure. Study subjects were asked to fixate on a distant target so as to enable examination of the central cornea. The central cornea was scanned in a single area at a desired depth. A drop of 0.5% moxifloxacin was instilled after the procedure. Image acquisition time was approximately 2 minutes per eye, and none of the subjects experienced any visual symptoms or corneal complications as a result of this examination. Both eyes were included for IVCM based investigations in the subjects of EDE cohort, whereas only one eye (right) was included for the control group.

Corneal Sub-basal Nerve Plexus and Dendritic Cell Density Assessments. An experienced masked observer selected five representative IVCM frames for corneal sub-basal nerves and dendritic cells image based analyses. Images of the sub-basal nerve plexus from the center of the cornea were assessed for each subject and for all the images the entire frame of 400 × 400 microns was used for analysis. Quantitative analyses of the nerve fibers were performed using Automatic CC Metrics software, version 1.0 (University of Manchester, UK). The parameters that were quantified included corneal nerve fiber density (CNFD), the total number of major nerves per square millimeter; corneal nerve fiber length (CNFL), the total length of all nerve fibers and branches (; corneal nerve branch density (CNBD), number of branches emanating from major nerve trunks per square millimeter; total branch density (CTBD) the total number of branch points per square millimeter; the nerve fiber area (CNFA) and the total nerve fiber area per square millimeter; and the corneal nerve fiber width (CNFW), the average nerve fiber width per square millimeter.[8-12] Dendritic cells (cells/mm^2) were quantified using Cell Count software (Heidelberg Engineering GmbH) by identifying bright individual dendriform structures with cell bodies in each image at the level of basal epithelium or at sub-basal nerve plexus.[13] The images were analyzed by two blinded observers and the average of the values was used for statistical analysis.

Statistical Analysis. All statistical analyses were performed with MedCalc^R version 12.5 (MedCalc Software bvba, Belgium) and GraphPad Prism 6.0 (GraphPad Software, Inc., La Jolla, CA, USA). Shapiro-Wilk normality test, Spearman correlations analysis and Mann-Whitney test were used for analyses.

RESULTS

Parameters such as TBUT, ocular surface disease index, corneal dendritic cell density (DCD), and corneal sub-basal nerve plexus features were measured and analyzed in controls and patients with EDE. The study subjects were age and gender matched. The ages between control (median 41 years; range 22–78 years) and EDE (median 44.5 years; range 19–73 years) cohort were not significantly different. TBUT was significantly lower in EDE subjects compared to controls. Total OSDI scores including discomfort and vision-related OSDI subscales were observed to be significantly higher in the EDE cohort. An inverse correlation was observed between TBUT with total OSDI score and discomfort and vision-related OSDI subscale.

The levels of cytokines, chemokines, secreted cell adhesion molecules, and pro-angiogenic factor in the tears of control and dry eye patients were studied using cytometric bead array. Of the various inflammatory proteins level quantified IL-1a, IL-1b, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12/IL-23p40, IL-12p70, IL-17A, IL-17F, CCL2/MCP-1, CXCL10/IP-10, ICAM1, IFNc, and VEGF were in the detectable range in the tears of both the healthy controls and patients. The tear levels of IL-1a, IL-1b, IL-6, IL-8, IL-12/IL-23p40, IL-12p70, CXCL10, and VEGF were not significantly different between the control and patient cohorts. IL-17A, IFNc, ICAM1, MCP1, IL-10, and IL-4 were significantly higher in patients with mild dry eye signs but with exaggerated symptoms compared to controls. IL-17F was also markedly higher though not significant (P 1/4 0.06) in the tears of these patients. In contrast, neuropeptide-Y and IL-2 were observed to be significantly ($P < 0.05$) lower in the patient cohort compared with that controls.

IVCM investigations revealed the presence of corneal dendritic cells (DCs) in EDE. Image based analyses revealed a significant increase in corneal dendritic cell (DC) density and subsets (DCs with and without dendritic processes) in the eyes of EDE patients compared to controls. Number of major nerves and nerve fiber width were significantly lower in EDE patients with moderate-to-severe OSDI score compared to controls. OSDI score, specifically pain or discomfort-related subscale, exhibited a positive correlation with total corneal DC density, as well as density of DCs with and without dendritic process in EDE patients subscale and corneal dendritic cell density in EDE patients. A significant association between the corneal DC density (total, with and without dendritic process) and various sub-basal nerve plexus features in EDE cohort was also observed.

DISCUSSION

The persistence of ocular pain and discomfort in a subset of patients with DED following standard therapeutic strategies as well as the lack of tear film metrics to predict this population poses a major challenge in the management of DED. It is therefore imperative to identify diagnostic modalities that can accurately predict patients whose symptoms may not resolve with conventional therapy or may require additional dietary or environmental interventions along with topical therapy to ensure a favourable prognosis.

IL-17, well known for its pathologic role in inflammatory disorders is involved in nociception by mediating mechanical allodynia by altering the expression of neuronal TRPV4 channels essential for

transduction of pain stimulus[14,15] was found to be higher in the tears of patients. Furthermore, a clinical trial (NCT01250171, www.clinicaltrials.gov/ct2/show/NCT01250171) reports a decrease in OSDI score in dry eye patient cohort on IL-17A blockers compared to IL-1b blockers or placebo controls. Similarly, an increased IFNc, MCP1 and ICAM1 observed in the patients could exacerbate the ocular symptoms, as they are reported to mediate pain.[16–18] Increased anti-inflammatory analgesic cytokines, IL- 4, and IL-10 observed in the patients could be a compensatory mechanism to counter the pro-nociceptive effects. However, it should be noted that IL-4 can stimulate ICAM1 expression that was also found to be elevated in patients. IL-2 known for reducing chronic neuropathic pain was found to be significantly reduced in the tears of patients, indicating a loss of the potential anti-nociceptive role of IL-2. Pain symptoms or hyperalgesia observed could be due to the direct effects of these inflammatory mediators which act by decreasing the sensory nerve thresholds in the ocular surface.

IVCM used to study architecture of the cornea in dry eye and other ocular conditions can provide additional predictive information such as corneal DCD and SBNP features which are altered in DED. In our study, we observed a significant association between OSDI scores, especially the discomfort subscale, with corneal DCD. Despite the absence of correlation between the decreased SBNP features and OSDI in EDE patients, we did observe a significant decrease in a subset of EDE patients with moderate-to-severe OSDI.

In our current study we have observed a significant decrease in various nerve features in EDE patients with moderate-to-severe symptoms, thus suggesting the use of corneal nerve morphological features as a predictor of the presence of pain in EDE patients. Neuropathic pain such as dysesthesias and hyperalgesia in dry eye patients can be due to either peripheral sensitization of neurons or damage to free nerve endings that interdigitate between superficial epithelial cells and are exposed to environmental and/or inflammatory stimuli. The presence of inflammation has also been found to directly and indirectly affect the structure and function of peripheral nerves resulting in altered nociception.[19] On the other hand excited nerve fibers can secrete neuropeptides which in turn trigger a neurogenic inflammatory response.

Dendritic cells play a role in immunomodulation and in antigen presentation and may influence pain pathways through their effect on T helper cells. In our study the significant increase in the corneal

dendritic cells observed in EDE patients was found to have positive association with the OSDI discomfort-related subscale scores and not vision-related OSDI scores. The current study also reports a differential association between corneal dendritic cells and SBNP features in EDE. Tuisku et al. demonstrated altered stromal corneal nerves and the presence of increased antigen presenting cells in patients with dry eye. They proposed that these changes were responsible for dysesthesia experienced by the patient in dry eye disease. In their study, however, they did not describe association between the dendritic cell density and changes in the corneal nerves.[20] We propose that an increase in inflammatory cells and the associated changes in sub-basal nerve plexus may be responsible for ocular discomfort experienced by patients in our cohort. Furthermore, an increase in the number of dendritic cells in close proximity to the sub-basal nerves was observed in patients with severe symptoms. Whether DC- mediated inflammatory or physical irritation of the nerve or changes in nerve physiology are responsible for pain in these patients needs to be determined. Therefore, this incidental observation warrants further investigation.

CONCLUSION

Altered pain mediators like neuropeptides and cytokines (molecular) and high corneal dendritic cell density or DCD (cellular) may underlie exaggerated nociception inevaporative dry eye (EDE).

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Deregulated Notch Signaling In The Lens Capsule Of Eyes With Pseudo Exfoliation Syndrome

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ABSTRACT

PURPOSE

Notch is a signaling pathway which regulates cell proliferation versus differentiation. It is vital for eye development, both in the lens and the retina. We hypothesized that altered notch signaling in the eye may account for differing phenotypes in pseudoexfoliation. This study aimed to identify the alterations in the expression of Notch pathway molecules in the lens capsules of eyes with pseudoexfoliation deposits.

METHODS

Anterior lens capsules were collected from 35 patients undergoing cataract surgery. These included patients with pseudoexfoliation syndrome/PXF (n=11), pseudoexfoliation glaucoma/PXG (n=7), primary open-angle glaucoma/POAG (n=8) and controls (n=9). Gene expression profiling for Notch pathway molecules was performed on the tissue using quantitative polymerase chain reaction. The results were confirmed by protein analysis using dot-blot or immune staining techniques.

RESULTS

There was no difference in the demographic characteristics of the 4 groups. There was an increase in the Notch 4 receptor expression (>15 fold) while decrease in Notch 2 expression in the PXF group as compared to the controls. Similarly, the Delta-like 3 and Delta-

like 4 ligands were significantly elevated in the PXF group as compared to the controls ($p<0.05$). Downstream targets HES 3 and HEY 1 expression revealed significantly elevated levels ($p<0.001$) in PXF lens capsules confirming a higher activity of Notch signaling in this cohort. Immunostaining also corroborated the gene expression profile.

CONCLUSION

Notch signaling is highly activated in the lens capsule of eyes with PXF, but not in PXG or POAG eyes. This may have an implication in the protective effect of activated Notch signaling in preventing glaucoma in eyes with pseudoexfoliation deposits.

KEYWORDS

Notch signaling pathway, Pseudoexfoliation, Pseudoexfoliation glaucoma

INTRODUCTION

The notch signalling pathway plays an important role in determining cell fate and regulating pattern formation in a wide range of tissues, which is essential for the orderly development of multicellular life.

The core components of Notch pathway in mammalian cells include (shown in Figure 1):

i. Ligands - Delta-like 1, Delta-like 3, Delta-like 4, Jagged 1, Jagged 2
ii. Receptors - Notch 1, Notch 2, Notch 3 and Notch 4
iii. Transcription factor of CSL family and downstream target genes - HES 1, HES 3, HES 5, HEY 1

Activation of this pathway occurs when a Notch receptor is engaged from a neighbouring cell via the Delta-like (DLL) or Jagged (Jag) ligands, as shown in figure 1. The Notch receptor undergoes proteolytic cleavage which liberates an intracellular domain (NotchIC); this then translocates to the nucleus and acts with transcription factors (also known as RBP-Jκ1, CSL, or CBF-1) to activate the transcriptional repressors.[1,2] Notch activation generally prevents differentiation and maintains progenitor or stem cell proliferation.[3,4] Notch signaling has diverse, outcomes, since it can inhibit, delay or induce differentiation determining the survival and fate of cells.

Low levels of Notch signaling decrease the neuro-protective function of glial cells in the postnatal retina.We hypothesized that altered notch signaling in the eye may account for differing phenotypes in pseudoexfoliation. This study aimed to identify the alterations in the expression of Notch pathway molecules in the lens capsules of eyes with pseudoexfoliation deposits.

METHODS

This was a prospective, observational study conducted at a tertiary eye care center between January 2016 to July 2017. The methodology adhered to the tenets of the Declaration of Helsinki for research involving human subjects. Written informed consent was obtained from all participants and the study was approved by the Institute's Ethics Committee.

Anterior lens capsules were collected from patients undergoing cataract surgery. These included eyes with pseudoexfoliation syndrome (PXF), pseudoexfoliation glaucoma (PXG), primary open-angle glaucoma (POAG) and controls. Control subjects were patients who had IOP < 21 mmHg, normal anterior segment examination apart from a cataract and normal posterior segment examination with non-glaucomatous optic discs, as assessed by glaucoma experts. PXF patients had clinical features of pseudoexfoliative material deposition in the anterior segment with IOP < 21 mmHg, non-glaucomatous optic discs and normal visual fields. PXG patients had clinically evident pseudoexfoliative material with IOP > 21 mmHg along with glaucomatous changes on optic nerve head examination as documented by glaucoma experts (neuroretinal rim narrowing, notching, and retinal nerve fiber layer defects), and/or visual fields changes. POAG patients had open angles on gonioscopy, IOP > 21 mmHg and glaucomatous optic disc or visual field changes. All participants were above 18 years of age. Eyes with a history of trauma or inflammation were excluded. All participants underwent acomprehensive ocular examination, which included a detailed medical history, slitlamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, dilated fundus examination, and ocular biometry (axial length and central corneal thickness).

The anterior capsules collected at the time of surgery were stored in 0.5 ml balanced salt solution at -80^0 C. Gene expression profiling for Notch pathway molecules (ligands, receptors and downstream genes)

was performed using quantitative polymerase chain reaction (PCR). Any over expression of RNA detected was confirmed by performing protein expression studies (dot-blot or immunostaining). The expression of Notch pathway molecules was compared between the groups using the ANOVA statistical test. Statistical analyses were performed using commercial software (Stata ver. 13.1; StataCorp, College Station Texas, USA). A P value of <0.05 was considered statistically significant.

RESULTS

Thirty-five eyes of 35 patients were included for the initial part of the study. The demographic details are shown in Table 1. The groups were well matched for age, axial length and central corneal thickness. However, comparison of the two glaucomatous groups showed the PXG eyes had significantly higher IOP and more advanced glaucoma (worse MD and thinner RNFL) than the POAG eyes.

The gene expression ligands, notch receptions and downstream genes were studied using PCR. Delta-like 3 (p=0.008) and Delta-like 4 (p=0.006) ligands were significantly elevated in the PXF group as compared to the other groups, as seen in figure 2.

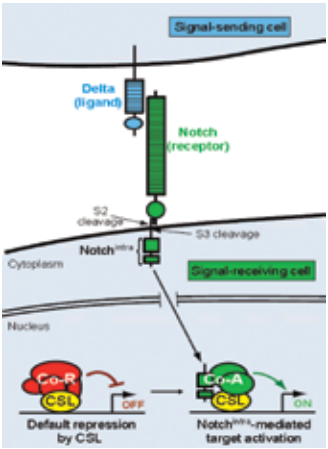

Fig.1: Notch signaling pathway showing Delta-type ligand, the receptor Notch and the CSL transcription factor

Table 1. Demographic and clinical characteristics of study participants

	CONTROL	PXF	PXG	POAG	P VALUE
No of Eyes	9	11	7	8	
Mean Age (SD)/ years	65.9 (9.6)	67.7 (5.9)	69.8 (9.7)	68.4 (3.5)	0.76
Mean IOP (SD)/ mmHg	14.9 (3.5)	16.3 (1.8)	21.6 (5.4)	16.5 (3.7)	0.006
Mean Axial length (SD)/ mm	23.4 (1.1)	22.8 (0.9)	23.0 (0.7)	23.6 (0.7)	0.23
Mean CCT (SD)/ µ	532.5 (40)	524.9 (40)	506.3 (37)	531.8 (28)	0.5
Mean mean deviation (SD)/ dB	-	-	-25.3 (4.06)	-4.2 (3.15)	<0.001
Mean Avg RNFL thickness (SD)/ µ	95.3 (13)	94.0 (11)	61.8 (8)	85.0 (8)	<0.001

The expression of Notch 2 receptor was significantly reduced while that of Notch 4 receptor was >15-fold higher in PXF eyes, as shown in figure 3.

HES3 and HEY1 expression was significantly elevated in PXF lens capsules ($p<0.0001$) as compared to the other groups, as shown in figure 4.

These findings were confirmed by analysing protein expression using dot-blot or immunostaining techniques, as shown in figure 5.

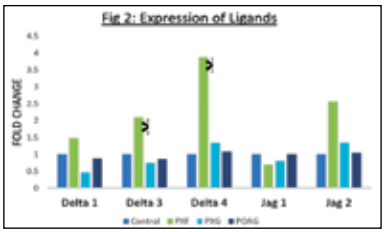

Fig.2: A graph comparing the expression of Notch ligands in controls, PXF, PXG and POAG subjects

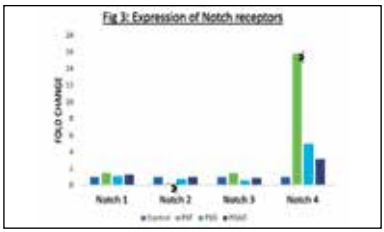

Fig.3: A graph comparing the expression of Notch receptors in controls, PXF, PXG and POAG subjects

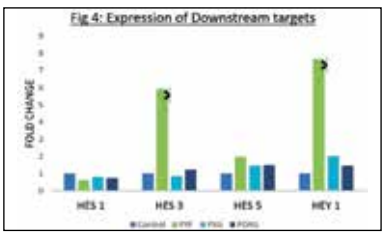

Fig.4: A graph comparing the expression of downstream targets in controls, PXF, PXG and POAG subjects

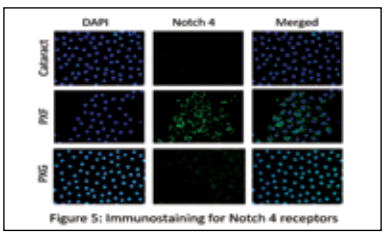

Fig.5: A slide showing immunostaining for Notch 4 receptors in PXF, PXG and controls

DISCUSSION

The present study shows the altered expression of Notch pathway molecules in the lens capsules of eyes with PXF as compared to those in PXG, POAG and controls. The role of notch signaling in the pathogenesis of pseudoexfoliation has not been previously explored.

Notch signaling has been shown to be essential for lens development by Rowan S et al.[5] They found that Jag1 ligand and Notch 1/2 receptor domains overlap significantly in the lens pit, during lens development. This finding has been supported by other studies as well, which have reported expression of Notch 1, Notch 2, and Jag 1 in the developing

lens.[6-9] Regarding the role of downstream targets, Jia et al. propose Hey1 as a major Notch effector gene, while Rowan et al believe in the strong expression of Hes1 throughout lens development.[10]

Besides the lens, the Notch pathway in the posterior segment has also been evaluated.Ghai K et al showed that low levels of Notch signaling is associated with reduced neuroprotective function of the Muller cells in the mature retina.[11]

In our study, we found that in PXF capsules, there was as increase in the expression of molecules of all the three components of Notch pathway, including DLL3 and DLL4 ligands, Notch 4 receptor as well as HES3 and HEY1 target genes. It suggests that Notch signaling is highly activated in the lens capsule of eyes with PXF, but not in PXG or POAG eyes. This may have an implication in the protective effect of activated Notch signaling in preventing glaucoma in eyes with pseudoexfoliation deposits. Further studies are required to elucidate the signaling intricacies in various ocular tissues with pseudoexfoliation.

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This Paper was judged as the **BEST PAPER** of **GLAUCOMA II** Session.

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Treating Refractory Glaucoma With High-Intensity Focused Ultrasound: A Safety Study

Dr. Neha Midha, Dr. Dada Tanuj, Dr. Srikant Kumar Padhy

ABSTRACT

PURPOSE

To establish safety of high intensity focused ultrasound (HIFU) in Indian population for treating refractory glaucoma.

METHODS

30 patients with refractory glaucoma and no visual potential were recruited. Patients underwent HIFU treatment using EyeOP 1 device, 6 sectors were treated for 8 seconds each. Primary outcome measure was to determine the incidence of device or procedure related adverse events and post procedure complications. Secondary outcome was to report the reduction in IOP and number of ocular hypotensive drugs being used.

RESULTS

The mean IOP before treatment was 33.56 ± 7.96 mmHg. The mean IOP (mmHg) at day 1, 7, 1 month and 3 months was 15.76 ± 7.75,

17.59 ± 10.66, 15.18 ± 3.56 and 18.32 ± 3.37.The no. of topical medications reduced from 2.9±0.99 before treatment to 2.1±1.1 at 3 months. No complication or major adverse effect linked with the procedure or with the device were observed except mild subconjunctival haemorrhage in 15 cases.

CONCLUSION

HIFU appears to be a safe procedure and has shown significant IOP reduction in treatment of refractory glaucomas.

KEYWORDS

cycloablation, high intensity focused ultrasound, refractory glaucoma.

INTRODUCTION

Glaucoma is a progressive neuropathy localized in the optic nerve that may lead to blindness, which progresses by the accelerated degeneration of the retinal ganglion cells, resulting, anatomically, in the excavation of the optical papilla and functionally, in a decrease of the visual field.

Numerous techniques using various physical agents have been used to reduce the production of aqueous humour by destroying the ciliary processes. The first difficulty is to determine the quantity of ciliary tissue to be destroyed, in order to efficiently reduce the IOP without inducing excess destruction which could then cause hypotony. The second difficulty is to selectively reach the ciliary processes without damaging the adjacent tissues. Trans scleral cyclo destruction with diode laser is the most used method in the world. This technique does not require opening the eyeball. The laser beam is transported via an optical fiber to a probe superimposed on the sclera surface approximately 1.2 mm posterior to the limbus. More recently, the endoscopic cyclo photocoagulation technique has been described. Visually controlled, this technique allows effective tissue coagulation to be achieved by using much less energy, thereby inducing less inflammatory reactions than laser diode. But this technique is a real "open eyeball" surgery.

The EyeOP 1 is a device using high frequency ultrasound to coagulate part of the ciliary body in a reproducible, non-operator-dependent manner, by creating lesions in a curve-shaped pattern distributed

over the whole circumference of the ciliary body without manipulation and eliminating the need for repeated and successive imprecise interventions. The device enables to perform a very accurate treatment via its centration and suction system, which secures the device on the eyeball and the high frequency ultrasound energy delivered. Indeed, the 21 MHz frequency enables to focus on targeted tissue (ciliary body) whereas crossed and surrounding tissue are preserved. The device also enables to perform a treatment without opening the eyeball (non-invasive treatment) and in a very short period of time, i.e. less than 5 min. Lastly, the user-friendly device enables to significantly reduce the learning period and the risks habitually associated with the acquisition of a new skill.

MATERIALS AND METHODS

It was a prospective interventional safety study. Patients with end-stage glaucoma and no potential vision (No perception of light or perception of light present with projection of rays inaccurate in atleast one quadrant) presenting to the Glaucoma Clinic/OPD shall be screened. Out of them, thirty patients meeting the following inclusion criteria were included in the study-

- IOP >= 21 mmHg without upper limit.
- Patient with no vision potential or blind eye
- Open Angle Glaucoma patients (Primary Open Angle Glaucoma (POAG) including Pigmentary Glaucoma (PG), Pseudoexfoliative Glaucoma (PXF), steroid responders and Neovascular Glaucoma (NVG), Angle Closure Glaucoma (ACG)
- Glaucoma patients whose IOP is not well controlled with 2 or more glaucoma medication
- Any patients with previous conventional glaucoma surgery failure (such as Trabeculectomy and/or Deep Sclerectomy), or end stage glaucoma patient indicated or contraindicated for conventional filtering surgery (e.g. Trabeculectomy).
- No previous intraocular surgery or laser treatment during the 90 days before HIFU Day
- Age > 18 years and < 90 years
- Able and willing to sign the informed consent form and complete postoperative follow-up requirements.

Exclusion criteria were as follows

- History of cyclodestructive procedures (cryotherapy, diode laser cyclodestruction, and endo-photocoagulation)
- History of ciliary body surgery
- History of ocular or retrobulbar tumor
- Ocular infection within 14 days prior to the procedure of Ultrasound CiliaryPlasty
- Eyes with implantation of glaucoma drainage device
- Congenital glaucoma
- Neovascular glaucoma with hyphema and/or vitreous hemorrhage
- Structure abnormalities in anterior segment which lead to excessive scleral expansion or change of ciliary body location
- Ocular disease other than glaucoma that may affect assessment of IOP (choroidal hemorrhage or detachment, lens subluxation, thyroid ophthalmopathy, and retinal detachment)
- Any other systemic illness as per investigator's discretion which will jeopardize patient's participation in the study.
- Any patient participating in another drug or device study

Patients scheduled to have glaucoma treatment with EyeOP1 were asked to give voluntary consent by signing the consent form for participation in the study and collection of data for this study.

Procedure: After peribulbar anaesthesia, the positioning cone is placed in direct contact with the eye, which allows for proper positioning of the transducers in terms of centering and distance. At the base of the cone, a suction ring allows a low level vacuum to be applied and enables one to maintain the cone in contact with the eye. The probe containing six active piezoelectric elements is inserted in the upper part of the positioning cone. The cavity created between the eye, the cone and the probe (4 ml) is filled with room temperature saline solution. The six transducers are placed at regular intervals on the upper and lower circumference of the ring, avoiding the nasal and temporal meridians, and oriented to create a focal zone consisting of 6 regularly distributed elliptical cylinder-shaped volumes.

Device models with different ring diameters, equipped with the 6 transducers, are available. In each patient, the probe model whose

focal zones actually matched the ciliary body is determined via ultrasound biomicrosopy (UBM) imaging or Anterior Segment OCT (Optical Coherence tomography) performed before the treatment, or using biometric anatomic parameters such as white-to-white and axial length measurements.

The probe is connected to the control unit which allows each of the 6 sectors to be sequentially activated according to the program. We treated 6 sectors for 8 seconds each with an interval of 20 secs between each sector.

After ultrasound treatment, appropriate anti-inflammatory (steroids eye drops for duration of 3-4 weeks) were prescribed. Other medications, such as antibiotic eye drops or pain killers were prescribed as necessary. All anti glaucoma medications were continued as before.

Patients were followed on day 1, 1 week, 1 month and 3 month. At each follow up complete ocular examination and IOP measurement was done and documented. All IOP measurements were done at same time of the day. On follow up the topical drugs were reduced if IOP was believed to have fallen below the target level.

Safety and Efficacy/Outcome assessment

a) Primary outcome: Safety - Incidence of all device and or procedure related adverse events during the study (Intraoperative and Postoperative)

b) Secondary outcome: Efficacy – Reduction of IOP
   - Mean IOP (mmHg) at each follow-up visits compared to the baseline IOP.
   - Number and mean number of ocular hypotensive medications used at each follow-up visits

RESULTS

Total 30 patients meeting the inclusion criteria were recruited in the study. Seven patients were lost to follow up. A total 23 patients who completed the follow-up protocol were enrolled for statistical analysis. 21 out of 23 patients responded to the treatment i.e. a success rate of 91.3% was noted in our study. The distribution of cases was as follows- Post vitreoretinal surgery (n=6, 26.08%), Post traumatic (n=5, 21.7%), Primary angle closure glaucoma (n=4, 17.39%), Steroid induced glaucoma (n=3, 13.04%), Combined mechanism glaucoma (n=1, 4.34%), Aphakic glaucoma (n=1, 4.34%), Pseudophakic glaucoma (n=1, 4.34%),

Post Penetrating Keratoplasty (n=1, 4.34%) and Primary congenital glaucoma (n=1, 4.34%). The mean IOP before treatment was 33.56 ± 7.96 mmHg. The mean IOP (mmHg) at day 1, 7, 1month and 3 months was 15.76 ± 7.75, 17.59 ± 10.66, 15.18 ± 3.56 and 18.32 ± 3.37 respectively. Anti-glaucoma medication was gradually tapered over 1 month. 9 patients were on oral acetazolamide before treatment. At 1 and 3 months, none of the patients required oral therapy. The number of topical medications reduced from 2.9±0.99 before treatment to 2.1±1.1 at 3 months. 14 out of 23 patients had mild subconjunctival hemorrhage due to placement of suction cone. No serious complication or major adverse effect linked with the procedure or with the device (severe hypotony, phthisis of the eyeball, scleral perforation) were observed.

DISCUSSION

Glaucoma treatment, be it medical, surgical or via physical agent, mainly aims at reducing the intraocular pressure (IOP) and slowing down the progress of the disease. Two main strategies that are presently implemented are: first, to restore sufficient drainage of the aqueous humour and second, to reduce the production of aqueous humor. Reduction of aqueous production is by administration of eye drops (medical treatment) or by destruction of part of the ciliary body, by using physical agents (laser, cold, ultrasound, etc.). The technique being used in this study pertains to the second strategy for the treatment of glaucoma: to reduce the production of aqueous humour via well-controlled thermal coagulation of part of the ciliary body, in a single step, using High Intensity Focused Ultrasound.

Many clinical studies have shown that the current laser methods of cyclodestruction are usually effective, but poorly tolerated (pain, significant ocular inflammation, risk of over-dosing the treatment that may lead to hypotony and phthisis) and associated with a high risk of vision threatening complications.[1-6] These methods are therefore usually reserved for advanced glaucoma refractory to conventional treatments.

Ultrasonic ablation of the ciliary body for treating glaucoma has been extensively studied in the 1980's and early 1990's. Several animal studies and then clinical series have reported that high-intensity focused ultrasound (HIFU) is an effective method with favorable results in terms of IOP reduction.[7-13] Maskin et al achieved a 38.4 % IOP reduction 8 months after HIFU cyclodestruction in 158 eyes having refractory glaucoma using a commercially available device

(Sonocare Therapeutic Ultrasound System Model, Sonocare Inc., Ridgewood, NJ).[12] With the same device, Sterk et al obtained a 42.2% IOP reduction 3 to 4 months after HIFU cyclodestruction in 44 eyes with refractory glaucoma.[13]

The specific advantage of HIFU is that the energy can be focused through non-optically transparent media without uncontrolled energy absorption, thus reducing the effects on the adjacent tissues. Similarly, energy deposition and tissue heating at the focus site do not depend on tissue pigmentation, which may vary greatly, particularly in the ciliary body. HIFU allows for a defined and adjustable tissue volume to be heated and treated at any depth or location within the eye.

In a previous model named Sonocare, the transducer was a bulky and heavy - piezo ceramic of 80 mm in diameter - and attached to an articulated arm which had to be positioned manually using an imaging probe. The procedure was long (more than 1 hour) and complex, the use of HIFU for cyclodestruction with Sonocare was gradually abandoned in the mid 1990's. Moreover, scleral thinning or perforation had been reported, probably due to improper positioning of the transducer. More than 20 years later, the HIFU technology has considerably progressed and reached a maturity which has enabled the creation of the EyeOP 1 device. The objective was to reduce the production of aqueous humor via well controlled thermal coagulation of part of the ciliary body, in a single step, using High Intensity Focused Ultrasound. This miniaturized device has an ergonomic feature that makes the treatment of the eyeball much more accurate, simple and fast. Furthermore, this miniaturization has allowed us to securely position the device onto the eyeball via a centering and suction system ensuring accurate and reproducible operating procedure. Lastly, with this technology, the procedure can be automated with an increased level of safety for the patient.

Functional in vivo studies have demonstrated the efficacy of coagulation of part of the ciliary body with HIFU. Histological and macroscopic results published in 2010 by Aptel et al[14] have demonstrated the very good local tolerance of the treatment and the accurate and targeted destruction of the ciliary body.

In accordance with results of our study, various clinical studies have confirmed the tolerance and efficacy of the coagulation of part of the ciliary body with focused ultrasound. No complication or major adverse effect linked with the procedure or with the device (severe hypotony, phthisis of the eyeball, scleral perforation) was observed,

with a 40% average reduction of the IOP in responder patients. This ultrasound treatment allows for the IOP to be very significantly reduced in patients suffering from glaucoma, without complications or major adverse effects.[13-22]

A prospective multicenter study conducted in 5 University hospitals on thirty eyes of open angle glaucoma patients naïve of filtering surgery demonstrated that the ultrasound glaucoma treatment is an effective and a well-tolerated procedure to reduce IOP.[20] Intraocular pressure was significantly reduced from a mean preoperative value of 28.2 ± 7.2 mmHg (n=3.6 hypotensive medications) to 19.6 ± 7.9 mmHg at 12 months (n=3.1 hypotensive medications) (mean IOP reduction of 30%. No major intra or post-operative complications occurred during 1-year follow-up period.[20]

Clinical studies in Europe and India conducted with the second generation of probes confirmed the results published since 2011.

A multicenter study conducted in 4 academic glaucoma centers in Europe on 52 eyes of 50 patients demonstrated that the intraocular pressure was significantly reduced from a mean preoperative value of 24.7 ± 7.1 mmHg (n=3.0 hypotensive medications) to 17.1 ± 7.4 mmHg (n=2.7 hypotensive medications) at 6 months, with a mean IOP reduction of 47% in responding patients.[21]

A dose study has been conducted on 75 patients (comparison of two ultrasound doses – 8 seconds vs 10 seconds ultrasound activation per transducer) on open angle glaucoma patients. Intraocular pressure was reduced from a mean preoperative value of 23.3 ± 2.3 mmHg (n=0.5 hypotensive medications) to 15.4 ± 3.5 mmHg (n=1.0 hypotensive medications) at 6 months, with a mean IOP reduction of 33.6% in responding patients for dose "8 seconds", and from a mean preoperative value of 23.7 ± 3.4 mmHg (n=0.8 hypotensive medications) to 16.1 ± 3.5 mmHg (n=0.8 hypotensive medications) at 6 months, with a mean IOP reduction of 32.2% in responding patients for dose "10 seconds".[22]

Graber M et al suggested HIFU cyclocoagulation to be a safe and reliable alternative to filtering surgery in the management of chronic angle closure glaucoma among patients with a high risk of malignant glaucoma.[23]

Giannaccare G et al[24] in their multicenter study recruited 30 patients and showed at days 1 and 180, the mean IOP was significantly reduced (18.4 ± 7.2 and 20.2 ± 6.2 mmHg, respectively; all $p < 0.0001$). Group 3 patients (8-s ultrasound exposure time) showed a greater IOP

reduction than the other two groups-4s and 6s (-16.2±8.3 for group 3 vs. -8.8±6.6 for group 2 and -3.7±6.5 for group 1; p=0.02 and p<0.001, respectively). Qualified and complete success was achieved in 23.3% and 46.7% of patients, respectively; treatment failure was recorded in 6.6%.

To conclude HIFU appears to be a safe and effective procedure with no serious vision threatening complications. There are various limitations to our study most important being the short duration of follow up, no data on the effect of HIFU on visual acuity and no control group. A long term follow up study is needed before this modality can be used in treatment naïve eyes with good visual potential.

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Merits Of Conjunctival Frill Incision In Trabeculectomy-Induced Astigmatism And Patient Discomfort

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ABSTRACT

PURPOSE

To compare results of a novel "Conjunctival frill/smile incision" on surgically induced astigmatism (SIA) and patient discomfort vs conventional trabeculectomy in initial postoperative period.

METHODS

Sixty trabeculectomy cases were subjected to either conjunctival frill incision, performed 1.5-2.0 mm from limbus (Study group) or conventional fornix based conjunctival flap (Control group). Corneal astigmatism and suture induced discomfort was assessed by keratometry and a self-devised patient questionnaire respectively.

RESULTS

Both groups generated a "*with the rule*" SIA, which was 1.77vs 2.42 at 1 week and reduced to 1.27 vs 1.8 in study vs control group, after removal of sutures - both scleral flap releasable and conjunctival at 1 month. Patient *discomfort score*, revealed enhanced comfort in 37% patients (study group) vs 17% (control group) during early postoperative period. After 1 month of surgery, good comfort was regained in all cases.

CONCLUSION

This novel suturing technique results in reduced surgically induced astigmatism (SIA), patient discomfort during first month after trabeculectomy.

KEYWORDS

Conjunctival frill, Smile incision, Trabeculectomy, Astigmatism, Patient discomfort

BACKGROUND

Since introduction of trabeculectomy by Cairns in 1968,[1] trabeculectomy has undergone multiple modifications to increase both survival and safety of the procedure. Of these different modifications, type of conjunctival flap has been subject to much research. Conjunctival incision influences both bleb morphology and therefore bleb longevity. Comparative studies to determine differences between these two standard conjunctival incisions of fornix based and limbal based by Shuster et al,[2] Grehn et al,[3] Traverso et al,[4] and Brincker et al,[5] have documented similar IOP control and bleb morphology.

The preferred conjunctival incision in our setting over last decade has been fornix based after the key study of Khaw PT et al[6] with the authors reporting "ring of steel" formation at incision site of limbal based conjunctival flaps, being a risk factor for bleb failure and preventing posterior extent of bleb. However, the issues plaguing fornix based conjunctival flap (FBCF) have been – need for anchoring/ suturing of conjunctiva to limbusto prevent bleb leak and shallow anterior chamber. These anchoring sutures lead to patient irritation, tear film disruption and corneal astigmatism.This study was designed to evaluate a new modified conjunctival incision, a golden mean between limbus and fornix, called "conjunctival frill incision" or "*Smile incision*" so called due to its physical appearance on table.

PURPOSE

To compare results of a novel "Conjunctival frill/smile incision" on surgically induced astigmatism (SIA) and patient discomfort vs conventional trabeculectomyin initial postoperative period

MATERIALS AND METHODS

A prospective, double arm, pre- and post-interventional study included 60 trabeculectomy cases in patients with >18 yrs of age and excluded patients with evidence of any prior incisional surgery involving superior conjunctiva, dry eyes and prior vitreoretinal surgery. Corneal astigmatism and suture induced discomfort was assessed by keratometry and *self-devised patient questionnaire* respectively. The discomfort induced by conjunctival suturing was graded by a Likertscale as mild, moderate, severe depending on symptoms of watering, foreign body and blurring of vision. Tear Break Up Time (TBUT) used to assess for evaporative dry eye disease subsequent to derangement in ocular surface.

Patients were randomly divided into two groups, with one group was subjected to 'Smile conjunctival frill trabeculectomy' and second group to conventional fornix based trabeculectomy. All patients were followed up for minimal 6 months with IOP, bleb morphology (IBAGS grading on slit lamp plus AS-OCT), surgically induced astigmatism (automated keratometry) evaluated at follow up visits of week 1, week 2, 1 month, 3 months and 6 months. Tear break up time assessed at all follow up visits upto 3 months, and *Patient Discomfort Score* calculated at week 1, week 2, and 1 month.

SURGICAL TECHNIQUE

Peribulbar anesthesia without adrenaline, was given with proper care and minimal massage. Conjunctival incision was made 1.5 mm to 2.0 mm from limbus leaving a frill of conjunctiva attached. After adequately cauterizing the conjunctival bleeders, a scleral incision was made, in the form of an upward facing trapezium sized 4 by 3 mm. Superficial scleral flap was dissected till 1.5 mm of clear cornea. A side port entry was made 1-2 clock hours away from the margin of scleral flap and slow controlled release of aqueous was done while withdrawal, to prevent sudden hypotony. Intracameral pilocarpine was injected, followed by small amount of viscoelastic to tauten the iris. A bevelled anterior chamber entry was initiated with a 3.5 mm keratome, at base of scleral flap, at junction of blue grey zone. An inner sclerostomywas done with Kelly's punch at base of the scleral

flap and minimum of 2-3 punches were taken creating a sclerostomy measuring 1.5 mm by 1 mm. A peripheral iridectomy was then performed. The superficial scleral flap was sutured with two - three fixed sutures and two releasable sutures. (Fig 1)

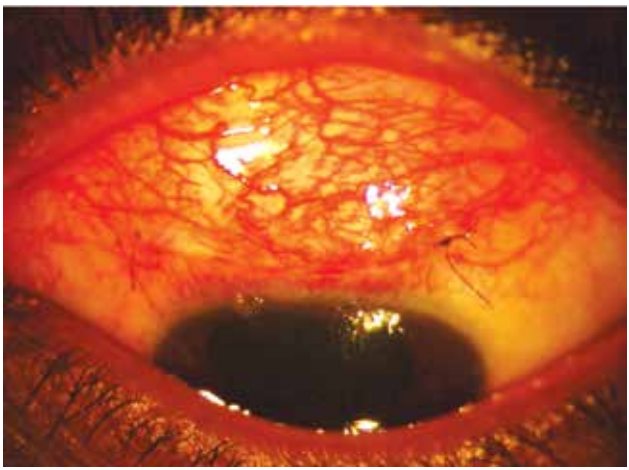

Fig 1: Slit lamp photograph of post smile incision trabeculectomy in immediate post-operative period

Conjunctiva was sutured in a running, horizontal mattress type, starting from one end with the suture knot resting away from the superior limbus. At end of surgery the bleb was raised by titration from side port.

RESULTS

The mean age was 41 ± 13 years (range 18-65 years) in study group and 49 ± 10 years (25-65 years) in control group. Both groups had almost similar sex distributions, male:female ratio 2:1. Glaucoma subtypes were heterogenous and equally distributed between angle closure glaucoma (25) and open angle glaucoma (24), followed by juvenile open angle glaucoma (8), secondary glaucoma (2) and iridocorneal endothelial syndrome (1) cases.

Surgically induced astigmatism (SIA)

Surgically induced astigmatism (SIA) of corneal origin was "*with the rule*" of a magnitude 1.77+ 0.8 vs 2.42 + 0.83 at 1 week in study vs control group. Study group documented a significantly less SIA versus control group ($p < 0.001$). Astigmatism was most pronounced during initial 2 weeks and reduced to 1.27+ 0.7 vs 1.8 + 0.8, (study vs control)

after removal of scleral releasable and conjunctival sutures by first month of follow up. Table 1 and Figure 2 depict the same.

Table 1: Surgical induced astigmatism (SIA)

SIA	Study group		Control		Intergroup difference (study vs control) Mann-Whitney U test
	Mean ± sd	Intragroup difference from Preop. levels Paired student t test	Mean ± sd	Intragroup difference from Preop. levels Paired student t test	
Preoperative	0.93±0.56	-	1.13±0.78	-	0.41
Week 1	1.77±0.8	<0.001*	2.42±0.83	<0.001	0.001#
Week 2	1.55±0.72	<0.001*	2.53±0.83	<0.001	0.001#
Post releasable suture removal					
1 month	1.27±0.65	<0.001*	1.78±0.77	<0.001	0.007
Post conjunctival suture removal					
3 months	1.09±0.57	0.006	1.47±0.8	<0.001	0.065
6 months	1.02±0.75	0.081	1.46±0.74	<0.001	0.035

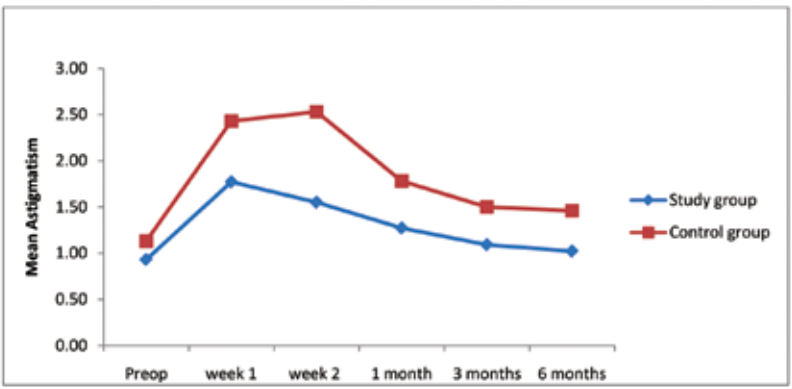

Fig 2: Surgically induced astigmatism trend over 6 months

Change in *vertical steepening* was highly significant in study group upto 2 weeks ($p<0.001$), which subsequently reduced over time whereas for control group this change in vertical steepening remained significant upto 3 months ($p<0.001$) follow up.

Though the *horizontal flattening* was noted in both the groups (study and control), change in horizontal keratometric values were insignificant in both the groups. (Table 2)

Table 2: Alteration in keratometry (vertical and horizontal meridian) over time						
	Vertical keratometry (mean change from preoperative)			Horizontal keratometry (mean change from preoperative)		
	Study group	Control group	Intergroup difference student t test	Study group	Control group	Intergroup difference student t test
Week 1	0.8	1.3	0.1	-0.03	0.015	0.86
Week 2	0.5	1.4	<0.001	-0.07	0.04	0.65
1 Month	0.16	0.74	0.01	-0.17	0.08	0.23
3 Months	0.26	0.32	0.8	-0.97	-0.01	0.06
6 Months	0.29	0.16	0.6	-0.025	0.09	0.8

Patient comfort

Patients with a functioning filtering bleb frequently complain of eye irritation, watering and foreign body sensation. Often blebs become large in size and height, leading to burning sensation and pain, a feature of *bleb dysesthesia*.

Patient *discomfort score*, measured by a self devised Likertscale in our study to assess ocular surface showed that "Smile technique/ conjunctival frill incision " (study group) led to significantly enhanced comfort in immediate post-operative period to trabeculectomy cases; subsequently comfort difference was minimal in the two groups. In the first week, 37% patients in study group had good comfort levels vs 17% in control group, found to be statistically significant (p value = 0.038). Fig 3 At first month follow up good comfort was regained in almost all cases irrespective of type of conjunctival incision.

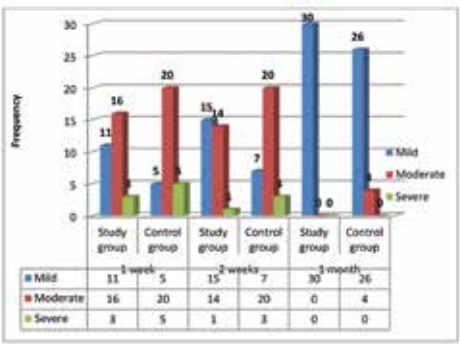

Fig 3: Patient discomfort score

Tear break up time

Tear disruption measured by TBUT, did not result in significant tear instability at any time during the postoperative period. It remained greater than 10 sec at 10.63 + 0.6:: 10.43 + 0.9 in study vs control group. This minimal disruption was most likely due to our practice

of using frequent lubricant drops in the postoperative trabeculectomy cases.

DISCUSSION

Surgical induced astigmatism (SIA)

Post-operative astigmatism is one of the most important causes for diminution of vision after trabeculectomy. Hugkulstone et al in 1991 investigated changes in corneal astigmatism after trabeculectomy and reported a reduction in vertical corneal radius, inducing SIA of "*With the rule*" (*WTR*) astigmatism upto a follow up of 7 weeks.[7] Kook et al in 2001 studied SIA over a longer follow up of 12 months period and reported "*With rule astigmatism*"(*WTR*) at 3 months, followed by an "*against the rule*" (*ATR*) shift at 1 year.[8] Claridge et al used computer-assisted corneal topography to document surgically induced astigmatism (SIA) after trabeculectomy and reported superior steepening of corneal curvature in majority , which they attributed to tissue contraction around the trabeculectomy site secondary to extensive scleral cautery. This finding was echoed by Rosen et al[9] and Vernon et al.[10] Dietze et al, mentioned the possibility of tight sutures and suggested a "posteriorly placed wound gape" from the internal sclerostomy as the cause.[11] Cunliffe et al (1992) in addition suggested that the internal sclerostomy allowed corneal edge of trabeculectomy to sink slightly thereby decreasing vertical radius of cornea.[12]

This surgically induced astigmatism is invariably corneal in origin and occurs more with use of corneal anchoring of conjunctiva, as required in fornix based conjunctival flap. As our study group involved conjunctiva to conjunctiva continuous suturing, without the suture being passed through cornea tissue, the resultant astigmatism was expected to be less. In addition, the astigmatism reduced after removal of both releasable and conjunctival suturing. Thus, only corneal astigmatism by keratometry was assessed.

The SIA in study group was found to be significantly less compared to control group using Mann Whitney U test with p values < 0.001 at week 1 and 2 and $p < 0.007$ at month 1.On further evaluation change in vertical and horizontal meridian over time vertical steepening noted evident of *With the rule astigmatism(WTR)* most pronounced at week 2 and 1 month. The reduction in astigmatism was noted on further follow up maximum at 1 month and minimal thereafter, the prescription of glasses should therefore be delayed till 1 month; the same has been postulated by Delbeke et al who have reported

stabilization of astigmatism at 3 month postop.[13] The reduction in SIA was steep for study group with minimal astigmatism induced, resolving within 2-4 weeks, whereas for control group the SIA declined sharply in first month and slowly thereafter with decline continuing till 3 month. This would imply that "*Smile incision*" *induces less SIA and causes more rapid resolution after suture removal*.

Tear break up time

Mendes C et al studied tear instability post filtering surgery and reported significant reduction in tear break up time after surgery.[14] Ji H et al in a cross-sectional study documented Dry Eye Disease (DED) to be relatively more common in patients with functioning filtering blebs following trabeculectomy than control group.[15]

No published study so far has evaluated tear instability in trabeculectomy cases based on type of conjunctival incision, to the best our knowledge. Tear disruption (assessed by BUT), was expected to be less for study group with no anchoring suturing. However, our study results did not corroborate this hypothesis since BUT values at 1 week and 1 month did not differ significantly between two groups although tear disruption was less in study group. This may be explained by the fact that our trabeculectomy cases are prescribed frequent lubricants during the immediate and intermediate post op period, which could mitigate dry eye effect subsequent to tear film disruption by suturing.

Patient comfort

In our study 37% (11/30 patients) in study group documented good comfort level versus 17% (5/30) in control group at 1st week follow up. After suture removal, in both groups the comfort level improved; to 50% in study group and 23% in control group. This indicates a significant improvement in comfort score in immediate post- operative period in patients with *Smile incision vs* fornix based incision. At 1 month follow up, good comfort was regained in almost all patients irrespective of type of suturing in 87 - 100% cases. This finding implied that *Smile technique/conjunctival frill incision* gave more comfort in immediate post-operative period to trabeculectomy cases in the initial fortnight; subsequently comfort difference was minimal in the two groups. To the best of our knowledge no prior study has evaluated patient discomfort post trabeculectomy

CONCLUSION

This novel suturing technique results in reduced SIA, patient discomfort during first month after trabeculectomy and is equally effective in

intraocular pressure (IOP) control. Reduction of surgical time and corneal distortion are further benefits of this technique. Thus, this technique can be easily adopted for trabeculectomy especially in eyes with no prior intraocular surgery.

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This Paper was conferred with the **AIOS - COL. RANGACHARI AWARD** for the **BEST PAPER of ALL SESSIONS (JOINT AWARD).** This paper was also judged as the **BEST PAPER OF INFLAMMATION** Session.

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A Novel Method For Predicting Retinopathy Of Prematurity (ROP) Blindness From The TEARS Of Infants

Dr. Anand Vinekar, Dr. Shivani Sinha, Dr. Chaitra Jayadev, Dr. Shetty Bhujang K

ABSTRACT

AIM

To correlate proangiogenic and inflammatory factors in the TEARS of infants with ROP

METHODS

TEARS from 44 infants undergoing ROP screening were analysed using cytometric bead array for a) proangiogenic factors: VEGF-A, angiogenin and fractalkine, b) adhesion molecules: VCAM-1 & ICAM-1 c) inflammatory mediators: IL-6, IL-8, RANTES & MCP-1. Two gestational age-matched cohorts: Any stage ROP & No ROP was correlated with the TEAR results

RESULTS

Higher levels of TEAR VEGF, Angiogenin, MCP-1 & RANTES ($p < 0.001$) were observed in the FIRST visit of infants who spontaneously regressed compared to higher stages of ROP. IL-6 showed an inverse trend. TEAR VEGF ($p < 0.001$) and MCP-1 ($p<0.05$) levels at FIRST visit were lower in infants who developed ROP later than controls

DISCUSSION

Non-invasively collected TEARS during the FIRST ROP screening visit has key biomarkers that can predict progression of disease. This will aid risk stratification, clinical triage and reduction in ROP blindness

INTRODUCTION

Approximately 60,000 children globally are blind due to retinopathy of prematurity (ROP). Developing countries like India and Latin America are facing the third epidemic of ROP. The incidence of ROP was found to be 41.5% and 26.4% of these eyes were type 1 ROP in a rural district NICU. The gold standard of ROP is shifting from indirect ophthalmoscopy to wide-field photo documentation but both of them require multiple sessions before a clinical conclusion is reached.

Angiogenic and inflammatory pathways plays a role in development of ROP. Association of various cytokines with ROP have been studied in vitreous, serum and cord blood. Cytokine levels of IGF 1 and VEGF have been found useful in predicting the risk of ROP. But invasive procedures are required to acquire these body fluids. The need of a non invasive easy screening test to determine at risk babies is warranted to aid in management of ROP

Tears have long been used as a biomarker in various systemic diseases like multiple sclerosis, Parkinsons disease, Tay Sachs disease and even in breast cancer. Tears have been used to study the role of various cytokines in keratoconus and dry eye disease as well and has helped in modulation of treatment strategy. In diabetic retinopathy tear levels of TNF alpha have been used to predict the severity of disease.

The tears have not been yet used to evaluate the various angiogenic and inflammatory cytokine levels in ROP or for predicting the infants at risk of developing ROP. The study aims to evaluate the role of tears in predicting ROP in infants as a non invasive novel method.

METHODOLOGY

Study design and clinical examination

The prospective longitudinal study was approved by the Narayana Nethralaya Institutional Review Board (IRB) and Ethics Committee. The guidelines followed were in accordance with the tenets of the Declaration of Helsinki. Study Subjects were recruited for the study after obtaining informed written consent from parents or guardian of the infant. Study subjects were the infants undergoing routine ROP screening according to the Indian national guidelines in the KIDROP programme. The infants were followed up until a favorable outcome was achieved. The favorable outcome was taken either as complete vascularization of the retina or regression of the stage of ROP. All the screening sessions were imaged using Retcam (Clarity MSI, USA).

A total of 44 patients were recruited and were divided into two groups. Group 1 consisted of 23 infants with any stage ROP eight infants each in Stage 1 and Stage 2 ROP and seven infants in stage 3 ROP disease respectively. Sixteen infants were categorized as group 2 consisting of 16 controls further classified as infants with immature retina in zone 3 (n=8); immature retina in zone 2 and zone 3 (n=6) and almost fully vascularized (vessels entering zone 3 but not reaching the ora serrata (n=2)

Tear sample collection

Tear samples were collected using Schirmer's strips by following Schirmer's test I protocol at every screening visit. Tear analytes were extracted from Schirmer's strips by cutting them into small pieces, agitation in sterile phosphate buffer solution (PBS) for 2 hours at 4°C followed by centrifugation.

Measurement of angiogenic factors, cytokine and chemokine

The levels of various inflammatory and angiogenic factors in the tears were measured using cytometric bead array (BD CBA Human Soluble Protein Flex Set System, BD Biosciences, Haryana, India) on a flow cytometer (BD FACS Calibur, BD Biosciences). The markers were chosen based on literature in ROP and its impact in retinal disease pathways. A preliminary analysis of these Cytokines were made and the ones detected were included. The CBA for this study was designed for simultaneous detection and quantification of angiogenic factors: Vascular Endothelial Growth Factor (VEGF), angiogenin; chemokines: Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES), monocyte chemotactic protein (MCP)-1, Fractalkine; cytokines: IL 6, IL 8 and adhesion molecule: L–selectin, Intercellular Adhesion Molecule 1 (ICAM1) and Vascular Cell Adhesion Molecule (VCAM).

Statistical analysis

All statistical analyses were performed with GraphPad Prism 6.0 (GraphPad Software, Inc., La Jolla, CA). Shapiro-Wilk normality test was used to check distribution of the data set. Mann-Whitney U test was used to analyze data.

RESULTS

The study cohort was equally distributed with respect to gender as well as at the age of the sample collection (Table 1, 2).

Table 1: Ttable showing distribution of gender in group 1 and group 2

	Female	Male	P value
Group 1	10	13	>0.05
Group 2	7	9	>0.05

Table 2: Table showing postmenstrual age at first visit and final visit in group 1 and group 2

	First visit	Final visit
Group 1	35 weeks 3 days	46 weeks 2 days
Group 2	34 weeks 6 days	40 weeks 1 day

Based on the subsequent second visit the study subjects were classified as infants with either progressing or regressing disease. Progressive disease referred to those infants who worsened to a higher stage of disease on subsequent second visit. Infants who showed resolution to a lower stage of disease were grouped in regressing disease. The angiogenic factors VEGF and angiogenin were both significantly upregulated in regressing compared to progressing stage ($p<0.001$) (Figure 1). The chemokines RANTES ($p<0.05$) and MCP 1 ($p<0.001$) were both upregulated in regressing when compared to progressing stage (Figure 2). The cytokines IL 6 and IL 8 do not follow a similar pattern, IL 6 was upregulated in

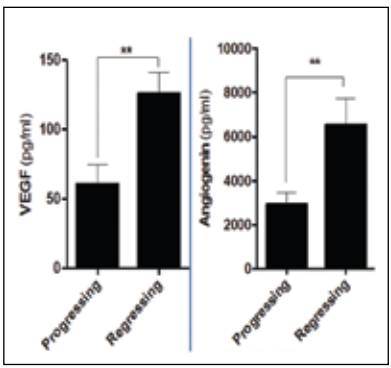

Fig.1: Bar graph showing levels of VEGF and angiogenin at first visit who progressed to a higher stage or regressed to a lower stage on subsequent second visit.

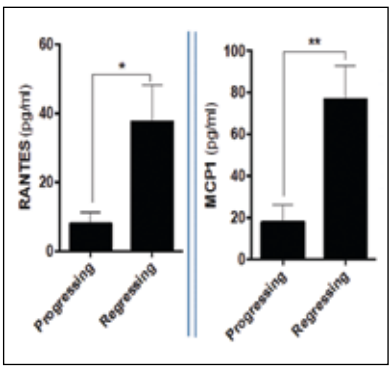

Fig.2: Bar graph showing levels of RANTES and MCP1 at first visit who progressed to a higher stage or regressed to a lower stage on subsequent second visit

progressing stage in contrast to IL 8 but it was not statistically significant (Figure 3). The other study parameters did not show a specific pattern and significant difference amongst groups.

The study subjects were further classified on the basis of second visit in three groups consisting of "non-ROP to non ROP" constituting controls, cases were further categorized as "non ROP to ROP" (infants who progressed from no stage ROP to some stage ROP on second

visit)and "ROP to ROP". The level of VEGF was higher in controls compared to the cases and was significantly higher when compared to non-ROP to ROP group ($p<0.001$) (Figure 4). Angiogenin was found to be high in ROP to ROP group compared to other group and was significantly higher compared to non ROP to ROP group ($p<0.001$) (Figure 4). All the three chemokines were lowest in non

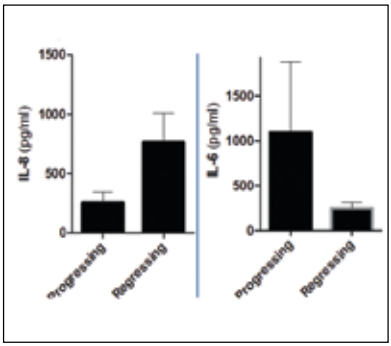

Fig.3: Bar graph showing levels of IL 8 and IL 6 at first visit who progressed to a higher stage or regressed to a lower stage on subsequent second visit

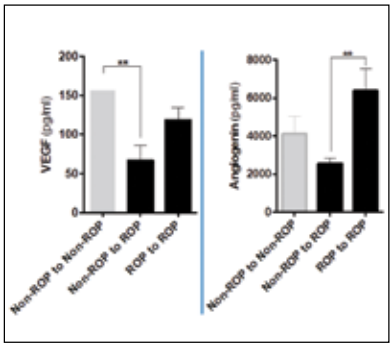

Fig.4: Bar graph showing levels of VEGF and angiogenin at first visit in controls (Non ROP to non ROP), infants who progressed from no ROP to some stage ROP and in subjects who had ROP at first visit

ROP to ROP group compared to other two groups. Only MCP 1 was statistically higher in controls compared to non ROP to ROP group (Figure 5). IL6 in contrast was lowest in ROP to ROP group and was statistically significant compared to controls(Figure 6). The other

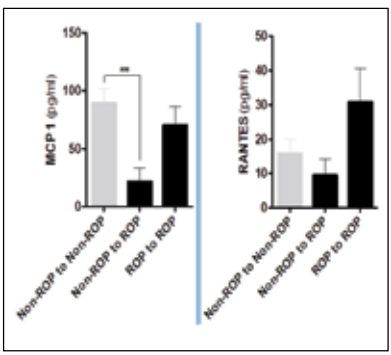

Fig.5: Bar graph showing levels of MCP 1 and RANTES at first visit in controls (Non ROP to non ROP), infants who progressed from no ROP to some stage ROP and in subjects who had ROP at first visit

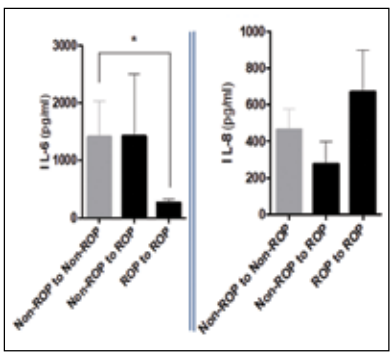

Fig.6: Bar graph showing levels of IL 6 and IL 8 at first visit in controls (Non ROP to non ROP), infants who progressed from no ROP to some stage ROP and in subjects who had ROP at first visit

study parameters did not show a specific pattern and significant difference amongst groups.

DISCUSSION

This is the first prospective study taken in infants with ROP to evaluate the role of tears in predicting at risk babies of developing the disease.

The main findings of the study is being enumerated as follows:

1 The levels of angiogenic factors i.e VEGF and angiogenin were elevated in patients who showed a resolution of disease stage compared to the progressing stage. This reflects presence of more angiogenic factors in a maturing retina which is in contrast to the fact that a maturing retina must express less of angiogenic factors

2 The chemokines RANTES and MCP 1 followed a similar pattern. The chemokines functions as chemo attractant as well as angiogenic factors and thus aid in neovascularization. RANTES have been found to be elevated in the first month after birth.

3 The cytokine IL-6 and IL-8 both have a role in inflammation and ocular neovascularization. IL -6 is found to be increased in progressing stage rather than in regressing stage. The reverse is true for IL-8. The inverse behavior of IL-8 can be attributed to its disputed anti-angiogenic property.

4 Significantly low levels of VEGF were found in infants at first visit who later developed disease. Low level of VEGF at first visit can serve as a predictive tool for identifying infants at risk of developing ROP.

5 MCP 1 also had a similar pattern resembling VEGF.

6 Both angiogenic and inflammatory markers were increased in mature retina when compared to immature retina.

These contrasting results of higher levels of angiogenic and inflammatory markers in maturing retina can be due to normal angiogenesis present at various other anatomic sites in the early life of a neonate. Also, the levels of these factors differ with the post menstrual age as well. So, the tear levels may not represent the actual intraocular levels but the association is important to determine at risk babies of developing or worsening ROP.

The estimation of VEGF and inflammatory marker MCP 1 can be assessed at first visit to determine at risk babies of developing or

progressing ROP. This can aid us in determining the frequency of visit of these patient and an early intervention to further progression of disease process.

The study establishes a association between low angiogenic and inflammatory markers with the development of ROP. To establish temporal causal relationship a larger sample size is needed. As there has been no studies in ROP with tears, the relationship of these factors could not be determined with the actual intraocular milieu. The samples were also not paired for age. The other confounding risk factors like sepsis were not taken in account during analysis.

Angiogenesis is a balance between proangiogenic and angiogenic factors. Inflammation aids in normal angiogenesis too. The early acute imbalance as seen in ROP may lead to neovascularization. The study highlights the imbalance in the early postmenstrual age in form of low angiogenic and pro-inflammatory markers in the babies who subsequently developed ROP or worsened to a higher stage. This novel study demonstrates the feasibility of using tears in preterm infants undergoing routine ROP screening using non-invasive and easy to employ methods to obtain vital information about their team analytes which can be used for risk categorization, prognostication, and follow-up. This has provided us a new tool in the management of these tiny and precious babies.

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H Versus U Shaped Flap Technique Of External DCR - Comparative Evaluation Of Surgical Outcome With Respect To Surgical Time

Dr. Rashmi Kumari

ABSTRACT

AIM

To comparatively evaluate the surgical outcome of external dacryocystorhinostomy with two different flap techniques (H/double vs U/single) with respect to surgical time.

STUDY DESIGN

Prospective randomized comparative clinical study

MATERIAL AND METHOD

96 patients of primary NLD block were selected. 47 underwent the conventional DCR by 'H' Shaped flap and 49 by 'U' Shaped flap with suspension to the orbicularis. Success rate was evaluated by lacrimal patency to irrigation and surgical time was calculated from skin incision to skin suturing. Statistical analysis was done by Chi-square test, T-test and Fisher's exact test.

RESULTS

Success rate in groups A and B was 93.62% and 95.91% respectively. Surgical time difference between the groups was statistically significant with t =7.2031, p= 0.01 (<0.05) while difference in complication rate was not significant (X2 test=0.733 p=0.391).

CONCLUSION

External dacryocystorhinostomy with H flap has no added advantage over the U flap while the later technique is much easier and less time consuming with comparable success rate.

KEY WORDS

External DCR, flap techniques, patency, complication

INTRODUCTION

Nasolacrimal duct (NLD) obstruction, primary or secondary, is one of the important causes of epiphora.[1] Most common cause of primary NLD block is chronic dacryocystitis. It causes trouble some symptoms like watering and discharge sometimes severe enough to cause social stigma. Medical management gives only temporary relief and the treatment of choice is surgery. The operative approach to the sac may be external or endoscopic. In 1904 Toti first described the external approach and West described the endonasal approach in 1911.[2] The latter approach fell out of favour because of difficult visualization and endonasal access to the lacrimal sac. However, with the newer, rigid telescopes, these difficulties have been overcome resulting in a resurgence of the endoscopic technique. Need of specialised training and very expensive instruments has kept endonasal DCR at backfoot in developing countries where external dacryocystorhinostomy (DCR) still remains the gold standard surgical treatment for epiphora due to NLD block. The aims and objectives of DCR are two folds- to eliminate fluid and mucus retention within the lacrimal sac and to establish a low-resistance drainage pathway between the conjunctival tear sac and the nasal cavity, by conversion of the lacrimal sac into part of the lateral nasal wall. The procedure is a highly successful in managing epiphora due to nasolacrimal duct obstruction.[3] The reported success rate varies between 85% to 99%.[4,5] However, surgical procedure is not technically easy and requires considerable experience as well as operative time. The tedious and time taking nature of this procedure discourages even the trained surgeons from doing DCR especially when the operative load of cataract is high. This need urges for some modification in the conventional technique which could make it simpler, less traumatic and less time taking without compromising

the success rate. The aim of this study is to evaluate and compare the outcomes of the conventional external DCR with suturing posterior and anterior mucosal flaps (H shaped) and the modified technique of creating and suturing anterior flaps (U shaped) only with respect to operative time, intraoperative complications and success rate.

MATERIAL AND METHODS

A prospective randomized comparative clinical study was undertaken at Indira Gandhi Institute of Medical sciences, Patna for one year duration, from June 13 to July14. After taking approval from the ethical committee of the institution, 96 patients, more than 20 years of age,with primary acquired NLD obstruction with or without mucocele were selected to undergo external DCR. Patients with secondary nasolacrimal duct obstruction, failed DCR, canalicular and punctal occlusion, lower eyelid deformity (entropion, ectropion or lid laxity), nasal mucosal pathology (atrophic rhinitis, lupus etc.), bleeding diathesis were excluded from the study. All the selected cases underwent thorough anterior segment examination of each eye, with special emphasis on examination of lacrimal drainage system [puncta, swelling, tenderness, fistula, regurgitation on pressure over lacrimal sac (ROPLAS)] and eyelids. Fundus examination was performed for both eyes in every case. Lacrimal irrigation was done in all cases along with primary and secondary Jones dye test. ENT consultation to rule out gross nasal mucosal pathologies and physician checkup for surgical fitness was obtained in all patients. The cases were randomly divided into two groups by a computer generated system, A and B with 47 and 49 patients respectively.

Surgery was done under local anaesthesia. A curvilinear skin incision of 8-10 mm, corresponding to the anterior lacrimal crest was given, care being taken to avoid trauma to the angular vein. After blunt dissection of orbicularis and exposure of lacrimal sac, a 10 x 12 mm diameter bony window was created taking care to preserve the nasal mucous membrane intact. It is necessary to remove the anterior lacrimal crest down to the entrance of the nasolacrimal duct. The landmarks of bony ostium were anteriorly upto 5 mm from the anterior lacrimal crest, posteriorly upto posterior lacrimal crest, superiorly upto the level of medial palpeberal ligament and inferiorly upto the

beginning of nasolacrimal duct. The margins of osteotomy were made smooth. In group A a 'H' shaped incision was made through the medial wall of the sac so as to form anterior and posterior flaps of the lacrimal sac. The nasal mucosa was incised in similar fashion along the upper and then the lower limit of the oval opening in its full diameter. In this manner two flaps of nasal mucous membrane were formed which were fashioned further by excising the extra edges. Both anterior and posterior flaps were sutured to their counter flaps with 6-0 vicryl. In group B, an U shaped incision was made in the nasal mucosa and the sac to create only a single flap with excision of the remaining tissue which were later anastomosed with each other and then suspended to the orbicularis muscle to prevent sagging. The surgical wound was closed in layers. Orbicularis muscle was closed with 3-4 interrupted 6/0 vicryl sutures and the skin incision by interrupted 6/0 silk sutures and a firm pressure dressing was done after antibiotic ointment application. Postoperatively all patients were given oral and local antibiotics and nasal decongestants for one week. Follow-up examination was scheduled on the 1st, 7th postoperative day and thereafter 1st, 3rd and 6th months from the day of surgery.

Skin sutures were removed on day 7 postoperatively. At each follow up visit cases were examined for any complications such as wound gap, infection, granuloma formation, discharge, epistaxis etc. The surgical success was defined by anatomical patency of lacrimal drainage system on irrigation at final follow-up. Blocked syringing was considered as surgical failure. Statistical analysis was done using chi square test and Fisher's exact test.

RESULTS

Epiphora with or without discharge was the most common presenting complaint. Chronic dacryocystitis accounted for 89% cases, chronic dacryocystitis with mucocele for 7.5% and 3.5% were diagnosed as encysted mucocele (Table 1).

In Group A mean age of the patient was 37.13 (±11.52) years with a range of (21- 60). In Group B, mean age of the patient was 37.37 (±9.57) years with a range of (23 – 61) years. The age difference between the groups was not significant (t test= 0.111, p = 0.918). (Fig. 1).

By gender, the majority of treated patients 75 (78.12%) female, and 21 (21.87%) were male. In the group A, 36 (76.59%) patients were

Table 1: Lacrimal system drainage disorders by Groups

	Group A (n=47)		Group B (n=49)		Total (n=96)	
	n	%	n	%	n	%
Chronic dacryocystitis	42	89.3%	43	87.75%	85	88.54%
ChronicDacryocystitis with mucocele	3	6.38%	4	8.16%	7	7.2%
Encysted	2	4.25%	2	4.08%	4	4.1%

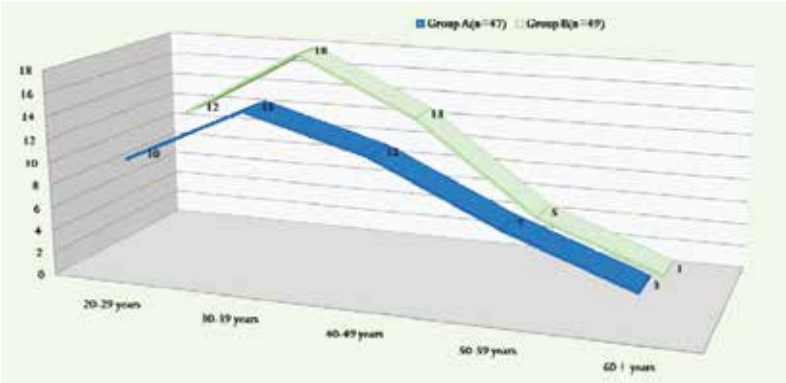

Fig.1: Fig.1 Age distribution, t test= 0.111, p = 0.918

female and 11 (23.40%) were male; while in the group B, 39 (79.59%) patients were female and 10 (20.40%) were male. Both groups have similar gender distribution without any statistically significant difference (X test=0,113; p=0,736). (Fig. 2)

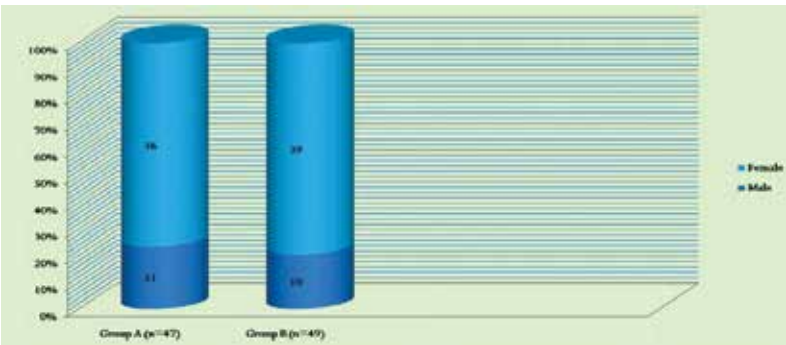

Fig. 2: Gender distribution. Both groups have similar gender distribution without significant difference (X^2 test=0.126; p=0.722)

Intraoperative haemorrhage was present in 5 cases (10.63%) in Group A and 7 cases (12.5%) in Group B (Table 2). Flap tear was present in 6 cases (12.76%) in Group A and 4 cases (8.16%) in Group B. The difference in complications between the two groups was not statistically significant (X test=0.733 p=0.391).

Table 2. Intraoperative complications in the two groups, (X test=0.733 p=0.391)

Complication	Group A (n= 47) No	%	Group B (n=49) No	%	Total (n=96) No	%
Un eventful	36	76.55%	38	77.55%	74	77.08%
Intra operative hemorrhage	5	10.63%	7	14.28%	12	12.5 %
Laceration and tear of flap	6	12.76%	4	8.16 %	10	10.41%

The overall rate of patency on lacrimal irrigation in external DCR was 94.79%. Of this success rate was 93.62% in group A and 95.91% in group B (Table 3). Recurrence of epiphora was present in 3 cases (6.38%) in Group A and 2 cases (4.08%) in Group B (Table 3). There was no statistically significant difference in success rate between the groups since the Fisher exact test statistic value was 0.674.

Table 3. Success rate in terms of patency and raecurrence

	Group A (n=47) No	%	Group B(n= 49) No	%	Total (n=96) No	%
Success rate	44	93.62 %	47	95.91%	91	94.79%
Recurrence of epiphora	3	6.38 %	2	4.08%	5	5.20%

Mean surgical time (calculated from skin incision to skin suture) in Group A was 52.14 min and in Group B was 43.39 minutes. Average surgical time taken was 8.75 min less in single flap technique in comparison to double flap (t =7.2031, p= 0.01) which was statistically significant (Table 4). p=0.722)

Table 4.Mean surgical time taken in the two groups.

	Group A (n= 47)	Group B (n=49)
MEAN (time in min)	**52.14**	**43.39**
SD	±4.42	±7.15
RANGE	44 -60	35- 58
SEM	0.65	1.02

DISCUSSION

Nasolacrimal duct obstruction is more common in females in 4th and 5th decade. According to Duke Elders the incidence of dacryocystitis in females is 75% to 80% and 20% to 25% in males. Jorgeet al. states that narrow lacrimal fossa in females predispose them to obstruction by sloughed off debris, due to hormonal changes that bring about a generalized de-epithelisation.[6] The mean age of study group in the present study was 37.25 years with standard deviation of 10.58 years. Out of total 96 cases, females 78.12% (75 cases) outnumbered males 21.8% (21) and the male:female ratio was 1:3.5. Our findings are in accordance with those of Deka et al who observed mean age of 41 years with 8.4 years standard deviation in their study of which 65% were females and 35% males.[7]

Similarly Kacaniku et al. reported mean age of the patients to be 44.6 years with 9.9 years standard deviation years, including 71% (37) females and 29% (15) males. The male:female ratio in their study was also 1:2.5.[8] External dacryocystorhinostomy is a highly successful procedure in managing epiphora due to nasolacrimal duct obstruction.[9] The reported success rate varies between 85% to 99% (Table 4). However, surgical procedure is not technically easy and requires considerable experience as well as operative time. Meticulous attention to atraumatic handling of the soft tissues, a clear, properly placed and uniform rhinostomy with smooth edges, careful dissection to

Table-5; Comparison of success rate of external DCR in different studies

Success rate	Double flap/ H Shaped	Single flap/ U Shaped
Serin et al	93.75%	96.67%
Elwan et al	90%	85%,
Katuwal et al	90.7%	87.5%
Pandya et al	73%	79%
Khan etal	97.3%	91.4%
Baldeschi et al	98%	100%
Ours	93.62%	95.91%

expose the true lumen of the lacrimal sac, followed by careful suturing of mucosal flaps, are important determinants of the outcome of the surgery. Moreover, individual response to tissue healing process is also an important factor for a successful DCR surgery.[10] In the present study, the overall surgical success of external DCR was 94.79%. Shun-Shin et al in their study combined the results of a total of 799 cases and showed an overall success rate of 91% for primary external DCR which is in accordance with this study.[11]

In current study 93.62% and 95.91% cases had favourable surgical outcome that were patent on lacrimal irrigation, in group A and group B respectively (Table 3). The difference between the two was statistically insignificant (p>0.05) which is in accordance with several other studies as shown in the Table 5. The difference in the success rate could be attributed to difference in sample size and different surgeon in different studies. However, Welham et al and Kansu et al have advocated that, both anterior and posterior mucosal flaps should be sutured, as this increases the probability of primary healing of the mucosal anastomosis and the tendency of primary and secondary haemorrhages and formation of granulation tissue is reduced.[12,13] In our study we found intraoperatively bleeding in 4 cases (5%), and nasal mucosal tear in 2 (2.5%) cases. The difference in complications in both groups was statistically insignificant (p=1.0). Kacaniku et al reported intraoperative bleeding in 3 (5.8%) cases and laceration of the nasal mucosa in 2 (3.8%) cases with statistically insignificant difference in their study groups which is in accordance with our study.[8] Most common post-operative complications were epistaxis and periorbital ecchymosis in 4 cases and 2 cases respectively in both the groups. The difference in complications in both groups was statistically insignificant (p=0.61). Deka et al reported five cases (3 cases of epistaxis and 2 cases of periorbital ecchymosis) with postoperative complications in their study.[7] Other complications were postoperative infection, canaliculitis, suture granuloma and wound gap one case each. This variation in types of complications could be attributed to individual response to tissue healing process rather than surgical intervention.

Mean surgical time taken in our study in H shaped flap technique was 52.14± 4.42 min and in U shaped technique was 43.39± 7.5 min, the difference being clinically significant .This result is in consistence with a similar study done by Agrawal et al.[14] Although they had more success rate with H shaped flaps in contrast to ours but the difference between the two groups was not significant as in ours. The overall surgical failure of external DCR was 10% in our study being 12.5% in group A and 7.5% in group B. All cases had non patent

lacrimal irrigation between 7th postoperative day and 4 weeks. Similar observations were made by Walland et al who reported a[15] failure rate for primary surgery as 12%. However failure rates ranging from 0 to 18% have been reported in several other studies.[11,13,14] These differences in failure rates with external DCR can be attributed to many factors including position and size of the ostium, common canalicular obstruction, scarring within the anastomosis due to infection or non-absorbable suture material, persistent mucocele, and the SUMP syndrome.[16] The surgical outcomes of both procedures were comparable in this study. Safe handling of posterior flap in double flap surgery in constrained anatomical field is difficult. Single (anterior) flap DCR is a safe, easy to master and effective surgical procedure for relieving epiphora without any significant intraoperative and postoperative complications.

CONCLUSION

Our study suggests that external dacryocystorhinostomy with suturing anterior and posterior flaps has no advantage over excision of the posterior flaps and suturing only anterior flaps with tenting it to orbicularis muscles. Later procedure is relatively easier to perform with less chances of flap tears and takes significantly less time.

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PRES Syndrome: An Important Cause Of Loss Of Vision In Patients With Acute Haemodynamic Instability

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ABSTRACT

The aim of the study is to evaluate PRES Syndrome as an important cause of vision loss in patients with acute haemodynamic instability. Patients with acute haemodynamic instability like acute pre-eclampsia/eclampsia/severe PIH/accelerated hypertension and presenting with sudden visual impairment were examined. Five patients in which the anterior segment was found to be normal, normal pupillary reactions and clear lens, with no major fundus

anomalies, were selected and sent for MRI of brain. MRI scanning showed T2 and FLAIR hyperintesities involving bilateral parieto-occipital regions in all the 5 patients, suggestive of PRES Syndrome.

Posterior Reversible Encephalopathy Syndrome (PRES), is an important cause of sudden painless visual loss in patients with acute haemodynamic instability and should be kept as a differential diagnosis when examining these cases. It is caused by vasogenic oedema, commonly in the parieto-occipital region, due to hyperperfusion.

KEY-WORDS

Posterior reversible encephalopathy syndrome, PRES, eclampsia, hypertension, sudden vision loss, parieto-occipital, vasogenic edema

KEY MESSAGES

PRES is an important cause of visual impairment in patients with acute haemodynamic instability like acute pre-eclampsia/eclampsia/severe PIH/accelerated hypertension. It is caused by vasogenic oedema, commonly in the parieto-occipital region. It is usually resolved completely with treatment of causative haemodynamic instability.

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES)[1,2] is a clinic-radiological entity that was well described by Hinchey et al[3] in 1996. PRES is characterized by variable associations of seizure activity, consciousness impairment, headaches, visual abnormalities, nausea/vomiting, and focal neurological signs. It occurs due to a number of causes, predominantly malignant hypertension, eclampsia, and medical treatments such as immunosuppressive therapy.[4]

Diagnosis of PRES relies on history, clinical examination, and radiologic findings of symmetric bilateral hyper-intensities on T2- weighted magnetic resonance imaging (MRIs) representing vasogenic edema. This edema most commonly affects the posterior occipital and parietal lobes.[5]

This syndrome is usually reversible once the underlying cause is treated or controlled. Management of PRES includes removal of any offending agents, blood pressure, and seizure management.[5]

The global incidence of PRES is unknown. It has been reported in patients ranging from 4 to 90 years of age, with most cases occurring

in young-aged to middle-aged adults. A marked female preponderance is observed which may reflect some of the underlying causes.[6]

PRES may cause sudden diminution of vision or visual impairment in a patient due to any of the above mentioned causes. The patient presents with a normal anterior segment and fundus examination does not reveal any relevant major abnormality and thus the diagnosis becomes difficult. This case series will help us understand the importance of PRES as a differential diagnosis when faced with such a clinical picture.

CASES

Patients presenting with complaints of sudden diminution of vision, and associated with acute pre-eclampsia, eclampsia, severe PIH and accelerated hypertension were screened in a tertiary care hospital from June 2016- May 2017.

Of these 5 patients were selected based on the following criteria:

Normal anterior segment.

No pupillary abnormality.

Normal Fundus.

Case 1- Female patient, 22 year old, primigravida, period of gestation 32 weeks, presented with complaints of sudden diminution of vision since morning. Patient didn't give any history of visual impairment till one day back. The patient's medical history was unremarkable. On examination, her blood pressure was found to be 170/100 mmHg. Proteinuria was present. The patient was diagnosed as severe pre-eclampsia. On ophthalmological examination, visual acuity was recorded as PL+ PR accurate in both eyes, the anterior segment and pupillary reflexes appeared normal.

Case 2- Male patient, 43 year old. Patient was a known case of hypertension and taking treatment since 5 years. Presented with complaints of giddiness and sudden diminution of vision. BP was recorded as 210/120 mmHg. The patient was diagnosed as accelerated hypertension. The visual acuity was recorded as PL-ve in both eyes. Anterior segment was normal and fundus examination showed grade 2 hypertensive retinopathy changes.

Case 3- Female patient, 27 years old, G2P2, period of gestation 34 weeks, presented with complaints of sudden diminution of vision since 1 day. Patient has a normal delivery previously and medical

history was normal. On examination BP was 150/100 mmHg. No proteinuria was present. The patient was diagnosed as having PIH (pregnancy induced hypertension). The Visual Acuity was recorded as CF 3M in RE and 6/60 in LE. Anterior segment was normal and fundus showed grade 1 hypertensive retinopathy changes.

Case 4- Female, 19 year old, primigravida, 28 week period of gestation. Presented with complaints of sudden diminution of vision since 3 – 4 hours. Patient had an unremarkable history. On examination the patient was found to be in altered sensorium. BP was 170/110. Proteinuria was present. The patient was diagnosed as having severe pre-eclampsia. The visual acuity was recorded as PL+ PR accurate in both eyes. Anterior segment was normal and fundus examination showed grade 1 hypertensive retinopathy changes.

Case 5- Female, 25 year old, G2P2, period of gestation 31 weeks, presented with complaints of sudden diminution of vision with hallucinations. The patient gave no prior history of similar complaints. BP was recorded as 180/100, and proteinuria was present. The patient was diagnosed as having pre-eclampsia. The visual acuity was recorded as PL-ve in both eyes. Anterior segment examination was normal while fundus examination showed grade 3 hypertensive retinopathy changes.

All these patients were sent for MRI scanning of brain to find out any neurological cause of visual impairment, the results of which showed T2 and FLAIR hyperintesities involving bilateral parieto-occipital regions, suggestive of Posterior Reversible Encephalopathy Syndrome.

They were started on respective anti-hypertensive medications to control their hemodynamic status, and BP monitoring and visual acuity was recorded at regular intervals.

After a period of 24-48 hours of start of treatment, the best corrected visual acuity of all 5 patients was 6/6.

MRI Brain of all these patients was repeated 1 week after start of treatment, and the results showed resolution of hyperintensities in all the cases.

Visual fields of the patients was tested using Zeiss Humphrey Visual Field Analyser after 1 week of start of treatment and found to be within normal limits in all 5 cases.

Table 1: Visual acuity of patients (by Snellen's Chart)					
	BCVA on presentation	BCVA at 6 hours after start of treatment	BCVA at 12 hours after start of treatment	BCVA at 24 hours after start of treatment	BCVA at 48 hours after start of treatment
Case 1	PL+ PR acc	CF 3M	6/60	6/6	6/6
Case 2	PL-ve	CF 1M	6/60	6/24	6/6
Case 3	CF 3m, 6/60	CF 3M, 6/36	6/36, 6/9	6/6,6/6	6/6
Case 4	PL+ PR acc	CF 3M	CF 3M	6/36	6/6
Case 5	PL -ve	PL+ve PR acc	CF 3M	6/6	6/6

Table 1: Visual acuity of patients (by Snellen's Chart)					
	BP at presentation	BP at 6 hours after start of treatment	BP at 12 hours after start of treatment	BP at 24 hours after start of treatment	BP at 48 hours after start of treatment
Case 1	170/100	160/90	150/90	140/80	140/80
Case 2	210/120	180/100	160/90	150/90	140/90
Case 3	150/100	140/90	140/90	130/80	130/80
Case 4	170/110	170/100	150/90	140/90	140/90
Case 5	180/100	160/90	150/80	150/80	140/80

DISCUSSION

Posterior reversible encephalopathy syndrome (PRES) is a rare neurotoxic state that presents with altered mental status, headache, seizures, and visual disturbances along with neuroimaging features of vasogenic edema involving the posterior cerebral circulation.

The most common visual abnormality is cortical blindness, but homonymous hemianopia, visual neglect, and blurred vision also occur.

Cortical visual impairment was noted in all 5 patients in this study. The resolution of patients' visual impairment and MRI findings after start of anti-hypertensives support the clinical diagnosis of PRES secondary to acute haemodynamic instability.

These symptoms are thought to result from cerebral edema. The mechanism behind the development of angiogenic edema and CT and MR imaging appearance of PRES is not known. Two opposite hypotheses are commonly reported: 1. severe hypertension leads to failing autoregulation, subsequent hyperperfusion, with endothelial injury/vasogenic edema; and 2. vasoconstriction and hypoperfusion lead to brain ischemia and subsequent vasogenic edema.[2]

The pathogenesis of this syndrome is poorly understood. Hypertensive encephalopathy is said to be the cause of this syndrome which has been demonstrated by various clinical and experimental studies.[7] Patients with hypertensive encephalopathy have the same clinical signs as those with PRES and they also have rapid resolution of clinical and imaging abnormalities once the blood pressure is lowered. The most widely accepted theory states that sudden elevation of blood pressure causes failure of autoregulation in the cerebral blood vessels leading to hyperperfusion, breakdown of blood brain barrier, and vasogenic edema.[8]

The syndrome is reversible, but early and prompt treatment is required to prevent complications like cerebral infarct, which may lead to permanent visual loss or other sensorymotor abnormalities.

Early recognition of PRES is important for prompt treatment by eliminating factors that cause PRES, such as uremia, hypertension, cytotoxic and immunosuppressive drugs.[9]

It is important for an ophthalmologist to recognize the symptoms and signs of PRES and correlate it the patients' other clinical findings. Various differential diagnosis of sudden diminution of vision in acute haemodynamic changes include optic neuritis, papilledema, central retinal artery occlusion and serous retinal detachment. It is important to differentiate PRES from these conditions.

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Structural And Functional Changes In The Retina And Optic Nerve In Cases Of Alzheimer's Disease

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INTRODUCTION

Alzheimer's disease (AD) is the most common dementia in the world and its incidence and prevalence are projected to double by 2050. Although conventionally Alzheimer's has been diagnosed clinically using cognitive battery and neuroimaging like MRI and PET, efforts are ongoing to detect Alzheimer's in the preclinical asymptomatic stage so that treatment or preventive strategies could be started at an earlier stage. In this regard, optical coherence tomography (OCT) has been studied over the past decade with some fruitful results. Our study evaluated a group of early stage Alzheimer's patients using ocular tests for structural imaging and electrophysiology to detect changes suggestive of disease.

METHODOLOGY

A total of 15 Alzheimer's patients were included in the study after being referred to our tertiary care centre from the Neurology department where they were screened for dementia using the Mini Mental State

Examination. The inclusion criteria was best corrected visual acuity better than 6/12, intraocular pressure less than 18, wilfulness to participate and cooperation towards tests. The Global Deterioration Scale was used to determine the disease severity. 15 age matched controls were selected randomly from the outpatient department patients and included only after ruling out any ocular, neurological or cardiovascular diseases. All subjects underwent extensive ophthalmological examination including visual acuity, intraocular pressure, colour vision, contrast sensitivity, anterior segment and posterior segment examination. Any subject found to have posterior segment pathology which may result in OCT or electrophysiological changes were excluded. Spectral domain OCT using Cirrus HD-OCT 4000 (Carl Zeiss Meditec, US) was performed to detect the retinal nerve fibre layer (RNFL) thickness with the Optic nerve 200x200 program and the ganglion cell layer (GCL) thickness and macular volume using the Macular 520x128 program. Sensitivity was kept at 50% for the effective data collection. Metrovision Monpack 3 vision monitor system was used to perform multifocal electroretinogram (mfERG) and pattern visual evoked response (pVER) for all patients. mfERG P1, N1 and N2 waves were evaluated. pVER P100 wave was evaluated. Descriptive statistics in the form of Mean ± Standard Deviation was used to analyse normally distributed variables. Pearson's correlation coefficient were used to determine any correlations among variables and the strength of such correlations. Data was considered significant when 2-tailed p value was <0.05.

RESULTS

The study evaluated 60 eyes of 15 patients and 15 controls. The demographic characteristics of the sample population is given in Table 1. The mean age of AD patients was 59.8 ± 6 .24 years (range 45-72). The median MMSE score in AD patients was 16 (range 10-23). The median duration of disease was 2.25 years (range 6 months-3.5 years).

Mean BCVA of patients was 0.183 ± 0.14, which was essentially normal. Mean contrast sensitivity was significantly reduced in the AD cases (1.4 ± 0.16) according to the Pelli-Robson chart. The anterior segment, intraocular pressure, fundus examination and colour vision were within normal limits in all subjects. Visual fieldswere evaluated for all cases and found normal. The RNFL, GCL thicknesses and the Macular volume measured using SD-OCT have been shown in Table 2.

Table 1: Demographic characteristics of AD cases and Healthy control subjects (mean ± SD)			
	AD cases (n=15)	Healthy controls (n=15)	P value
Age	59.8 ± 6.24	60.7 ± 7.96	0.73
Sex (M/F)	8/7	6/9	-
BCVA (logMAR)	0.183 ± 0.14	0.125 ± 0.13	0.25
IOP (mm Hg)	14.67 ± 2.84	14.87 ± 2.6	0.84
Contrast sensitivity	1.4 ± 0.16	1.85 ± 0.1	<0.001
			Median
Disease duration (years)			2.25
Mini Mental State Examination score			16

Table 2: Mean ± SD of SD-OCT parameters of nerve fiber layer, ganglion cell layer and macular volume			
	Cases (n=30)	Controls (n=30)	P value
Average nerve fibre layer thickness (um)	73.43 ± 12.74	86.04 ± 11.42	<0.001
Average ganglion cell layer thickness (um)	63.69 ± 14.77	84.99 ± 7.27	<0.001
Macular volume (cumm)	8.98 ± 0.84	9.75 ± 0.42	0.001

The electrophysiological data analysed in the subjects has been recorded in Table 3. RNFL and GCL thinning was observed in AD patients along with significant electrophysiological abnormalities (p<0.001).

Table 3: Mean ± SD of amplitudes of mfERG and pattern VER waves			
	Cases (n=30)	Controls (n=30)	P value
Average P1 amplitude (nV)	896.26 ± 239.67	1135.33 ± 234.83	<0.001
Average N1 amplitude (nV)	-471.87 ± 119.07	-609.01 ± 108.51	<0.001
Average N2 amplitude (nV)	-705.41 ± 209.66	-1040.57 ± 224.89	<0.001
p100 amplitude (µV)	7.62 ± 2.97	11.04 ± 2.89	0.015
Average P1 implicit time (ms)	48.57 ± 4.3	44.95 ± 2.05	<0.001
Average N1 implicit time (ms)	28.47 ± 4.53	2.44 ± 2.57	<0.001
Average N2 implicit time (ms)	65.28 ± 4.6	63.32 ± 5.2	<0.001
p100 latency (ms)	120.01 ± 6.99	108.36 ± 4.84	<0.001

The structural and functional changes of the retina and optic nerve were correlated with each other (Table 4). RNFL thickness changes significantly correlated directly with mfERG amplitude changes and inversely with implicit time. RGCL had a weaker yet significant correlation with the functional parameters. Pattern VER amplitude correlated directly with RNFL, RGCL changes and mfERG amplitudes

Table 4: Summary of correlation of structural and functional changes in the retina and optic nerve in AD patients		
	r	P value
	Average RNFL thickness	
Average P1 amplitude	0.65	<0.001
Average N1 amplitude	0.54	0.002
Average N2 amplitude	0.534	0.002
Average N2 implicit time	-0.384	0.036
P100 amplitude	0.737	<0.001
P100 latency	-0.368	0.046
	Average RGCL thickness	
Average P1 amplitude	0.374	0.042
Average N1 implicit time	-0.377	0.04
P100 amplitude	0.474	0.008
	P100 amplitude	
Average P1 amplitude	0.48	0.007
Average N1 amplitude	0.495	0.005
Average N2 amplitude	0.426	0.019
Average N2 implicit time	-0.719	<0.001
	P100 latency	
Average P1 amplitude	-0.397	0.03

significantly. Pattern VER latency correlated inversely with RNFL thickness and mfERG amplitude.

DISCUSSION

Several studies have evaluated the RNFL using time domain and spectral domain OCT machines and found global thinning in Alzheimer's patients.[1,2,3] Cheung et al evaluated the GCL separately and found thinning of the average GCL thickness in the macula.[4] Moschos et al evaluated the RNFL along with mfERG changes in AD patients and found a diffuse retinal electrical dysfunction, but they did not study the correlations between the different parameters.[5] Pattern VER has been found to be deranged in early stages of AD and it may represent an impairment in the anterior visual pathway function.[6] No study till date has evaluated the correlation between the structural and functional impairment present in Alzheimer's patients. Our study has observed that there is a conclusive evidence of correlation between the structural degeneration and the functional impairment of the neural component of the eye in AD patients and these tests may help in evaluation of mild cognitive impairment cases in future.

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This Paper was conferred with the **AIOS - OCULAR PATHOLOGY AWARD** for the **BEST PAPER** of same Session.

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Idiopathic Orbital Inflammation Of Orbit And Ocular Adnexa: Histopathological Analysis

Dr Dipankar Das, Dr. Kasturi Bhattacharjee, Dr. Jayanta Kumar Das, Dr. Deepika Kapoor

INTRODUCTION

Non-specific orbital inflammation affects orbital tissue including fats, lacrimal glands, extraocular muscles etc focally or diffusely.[1,2,3,4] Affection of Tenon's capsule is the least frequent location.[2,3,4] Incidence and prevalence findings of non-specific inflammatory disease of orbitbased on scientific literature was very difficult as it depended on inclusion or not of specific and non-specific inflammatory pathologies.[3,4,5,6,7,8]

Aim: To present histopathological analysis of idiopathic inflammatory disease of orbit and ocular adnexa

METHODS

Design-A retrospective laboratory based study.

The study was carried out in an ocular pathology laboratory in a tertiary institute of northeast India where analysis of 93 cases were done in 5 years between 2011 and 2016. Routine haematoxylin eosin and other special stains were done for the diagnoses. Immunohistochemistry (IHC) panel were also carried out. For infectious pathology, Grocott's methenamine silver (GMS) stain for fungus, tissue Gram's stain for bacteria's and acid fast stains for tubercular bacilli were done. IHC panels were done for CD 20 (B-cells), CD 3 (T-cells), CD 45 (Leucocyte common antigen, LCA), BCL 2, CD 138 (Plasma cells), Kappa, Lambda, IgG4 in tissue, IgG4 in serum etc. IHCs were done using kit methods (Standardized) and adequate controls were taken for each sample.

RESULTS

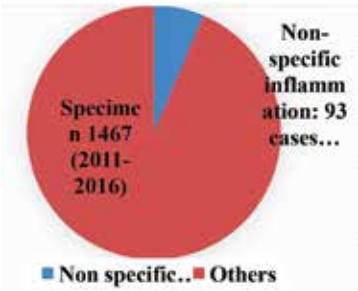

Fig.1: Graph showing non-specific orbital inflammatory cases in respect to total cases received in the ocular pathology laboratory during 2011-2016

93 cases (6.64%) of non specific orbital inflammation were reported out of 1467 specimens (Figure 1). Orbital pseudotumors (IOID) were seen in 27 cases (sclerosing variety-6); benign lymphoid hyperplasias in two cases; reactive lymphoid hyperplasias in 10 cases; plasma lympho-proliferative reactive lesions in four cases; IgG4 related disease in one case; non- specific inflammatory reactions (conjunctiva, sclera and lid) in 49 cases (Figure 2). In all the diagnoses, infections and lymphomas were excluded.

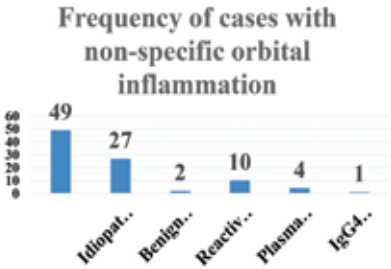

Fig.2: Distribution of Inflammatory disorders of orbit

DISCUSSIONS

Pathology of typical non-specific orbital inflammation were characterized by cellular infiltrate, vascular congested tissues, altered lacrimal gland tissue and disturbances in other orbital structures.[1,2,3,4] Grossly, the lesions displayed greyish white coloured tissues and microscopically, it revealed inflammation in the orbital structures and cellular infiltrates that were focal, multifocal or diffuse.[3,4] Cellular infiltrations were of differentiated mature lymphocytes, intermixed with plasma cells, eosinophils, polymorphs and rarely with histiocytes and macrophages.[1,2,3,4,5] The infiltrates were polyclonal and lymphoid follicles could be seen with germinal centres occasionally. The lesions were highly vascular due to capillary proliferations and were accompanied with perivascular and lympho-plasmacytic infiltrations and eosinophils were sometimes seen tracing near capillary adventitia.[1,2] Endothelial cells showed hyperplasia and sometimes there were reactive increase in the number of cells. In some long standing cases, sclerosing patterns were noticed and periductal fibrosis in lacrimal tissue with atrophied acini were seen.[1,2,3,4,5]

We had seen 93 cases (6.64%) of non specific inflammation reported out of 1467 specimens. IOID were seen in 27 cases (sclerosing variety-6 cases), benign lymphoid hyperplasias in two cases reactive lymphoid hyperplasias in 10 cases, plasma lympho-proliferative reactive lesions in four cases, IgG4 related disease in one case, non specific inflammatory reactions (conjunctiva, sclera and lid) in 49 cases (Figure 2). In all the diagnoses, infections and lymphoma were excluded from the cohort.

Moreiras and Prada et al. studied 189 cases of non-infectious inflammatory disorders (specific and non-specific) and found an incidence of 12.8 % among orbital lesions excluding thyroid orbitopathy.[1,7] Pseudotumours or non-specific inflammations were frequently diffuse variety in 30 cases, anterior in 20 cases, dacryoadenitis in 26 cases and myositis in 24 cases.[1,4,6,7,9] Our histopathological cases in the study were 6.64% which was almost half the above mentioned study.[7]

CONCLUSION

Biopsy supported study on non specific orbital inflammation was important to know the pattern. Further, larger multicentre studies will give better insight on the clinico pathological aspect of this inflammatory orbital disease.

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Mr. Apurba Deka, Technician, Ocular Pathology Lab, SSN, Guwahati, India

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A Novel Online Retinopathy Of Prematurity (ROP) Training Model For Rural India – "WISEROP.COM"

Dr. Anand Vinekar, Dr. Chaitra Jayadev, Dr. Shetty Bhujang K

ABSTRACT

AIM

To demonstrate the utility and impact of a novel online model for ROP training – "WISE-ROP"(Wide-field Imaging for Screening and Education of ROP)

METHOD

An indigenous, low-cost, high-impact, ROP training program was digitized (www.wiserop.com). The secure portal allowed trainees access to online course material, interactive video assessments and live mentor evaluation of imaging skills leading to certification based on the national guidelines. Cost impact compared to conventional training was assessed

RESULTS

Non-physician trainees from remote centers with no other access to ROP training successfully executed and completed the courses. There was 85% reduction in overall training costs and 10:1 'time to train' benefit

CONCLUSION

WISE-ROP is a unique model that can 'create' several imaging specialists for ROP screening in a short duration and at a lower cost compared to the conventional method. The program can help fill the void of screeners and improve access for rural infants

INTRODUCTION

In India over 35 lakh babies born are premature annually, leading all nations worldwide in the number who are born and survive. With this burden, the prevalence and risk of blindness from Retinopathy of Prematurity (ROP) has also increased. India is a facing the global 'third epidemic' of ROP. A high birth rate, declining infant mortality, improved survival of low birth-weight babies and lack of uniform neonatal care, increases the vulnerability of these babies to blindness.

Until recently, ROP in India was reported and believed to exist only in urban neonatal units with an incidence between 37- 54%. Our group has reported that rural and semi-urban centers in Karnataka have an incidence of ROP comparable to level 3 neonatal intensive care units (NICUs) of urban centers in the country. With fewer than 120 ROP specialists recently reported by the Indian ROP society who are trained to perform screening and appropriate laser treatment, there are millions of infants who are at risk of preventable blindness.

To address this lack of ROP screening service especially in the rural and outreach communities, our group developed a tele-ROP platform in 2007-2008, which continues to serve in rural and inaccessible areas

of the South Indian state of Karnataka.Under this program, namely the Karnataka Internet Assisted Diagnosis of Retinopathy of Prematurity (KID ROP), non-physician 'technicians' travel to different rural and semi-urban neonatal units on a fixed time table to perform ROP screening using digital imaging and the tele-ROP platform. The examinations are performed on-site, using a portable, wide field, digital retinal camera (Retcam Shuttle, Clarity MSI, USA or the Neo, Forus Health, Bangalore, India). The retinal images are uploaded on a secure, indigenous tele-ROP platform that is accessed by experts on their smartphones to provide real-time diagnosis.

The imagers have been hitherto trained using a validated program to not only image on site, but also to perform the first triage of diagnosis onsite itself to allow the result to be communicated to the rural mother or family so that appropriate counseling could be performed to allow better follow-up. The imagers are training is based on a 20 point score called the STAT score that has been previously published. The score and the process followed in KID ROP was validated by the Australian Government University in Perth using the Center for Disease Control (CDC) template in 2015 and has become the backbone of training scores of technicians, nurses, ophthalmic imagers and health care workers since.

With the availability of low-cost, indigenous, infant ROP cameras an increasing number of 'adopters' have created a new demand for trained, accredited and certified infant retinal imagers. However, the training takes 30,60 or 90 working days of on-site training with travelling of over 1000 kms in a week respectively to successfully complete Level I, II and III certification. With an increasing number of non-physicians requiring training in a short period of time, scaling this process was a challenge.

In this study we describe a novel, online training platform that was created to obviate the need for health care workers to travel to the city headquarters and to the outreach. The reduction in the duration of the training program, the efficacy of imparting theoretical and practical skill based learning and the cost benefit of such a program was evaluated.

METHODS

An online portal named "WISE-ROP" (Wide-field Imaging for Screening and Education of ROP), was created using a secure, internet based configuration. The portal provided secure access to registered users.

Prior to registration, assessment and quality control measures were developed. The candidates were selected based on the program criteria for ROP imaging screeners. Each candidate is assigned a mentor from the team. The mentors are currently part of the KID ROP team, and will expand to other region wise mentors in phase 2.

The enrolled candidates had access to four courses. Course 1: ROP basics. These were divided into several units, which detailed basic anatomy, disease specific anatomy, ROP classification, ROP screening and management. Course 2: Telemedicine for ROP in India, ROP screening guidelines for India, age terminology and metrics, logistics and documentation of ROP Course 3: Understanding imaging, Imaging on the RetCam shuttle, Imaging on the Forus Neo camera and Course 4: Assessment of Image quality, Uploading of images on the WISE-ROP portal, training validation and accreditation.

Each course is divided into lessons. Each lesson has a self-assessment quiz and a mentor-assessed quiz after each course is completed. Candidates may progress to the next course only after successfully completing the exit exam of each course respectively.

Live video based assessments are integrated on a "Google Hangout' template that is securely embedded into the WISE-ROP platform. Mentors and candidates are engaged in a unique one-on-one scheduled video classroom. During these session, practical demonstration of skills, modification of imaging techniques, soft-skills imparting, remote hand-holding methods and rote-recall methods were developed.

In this pilot project, selected candidates underwent a 7 day onsite (at headquarters) orientation program. During this period, they underwent hand-holding sessions on the retinal camera on mannequins and infants as per previously published protocols.

Post capture image processing, saving, reporting, uploading and archiving were also covered in the curriculum.

The time average duration for successful completion of the course were tabulated for the candidates and compared with profile matched candidates from the historical cohort who did not have online access. Direct and indirect costs incurred were tabulated for the course, travel and logistics and compared with historical data of the program when the entire training was performed on-site. International candidates using the portal were assessed using international monetary denominations consistent with their institute and job profiles.

The study was approved by the IRB of the institute and conforms to the Declaration of Helsinki. All patient information was anonymized. Only parents who consented for ROP screening using wide-field imaging were enrolled in this study.

RESULTS

Enrolled candidates were chosen from the voluntary Government centers under the KID ROP program and the non-governmental hospitals that have been beneficiaries of the program. These were ophthalmic assistants (3), optometrists (3), or ophthalmic imagers (3). In addition, seven female staff nurses form government neonatal units were chosen after an orientation program where 55 nurses attended. Four international candidates were also enrolled in the pilot phase of the program.

The average duration of completing the course was 88 days (+/- 3.2 days) for Level III in the traditional method and 9.8 days (+/- 7.4 days) ($p < 0.001$) in those using WISE-ROP. The mean cost to company (CTC) was amortized to account for the currency, time period (when historical data was used) and the shared costs of the infrastructure, content creation, copyright costs, online data management costs, internet charges, travel allowances, dearness allowances (as per Government regulations), accommodation, consumables, resource person surveillance visits and faculty mentorship. There was 84.6% reduction in the cost of the training program using WISE-ROP compared to the historical conventional method.

Fig. 2: Screen shot of the WISE-ROP module of the lesson on Retinopathy of Prematurity (Basic). The dashboard on the right shows the completed and pending lessons in each course

Fig. 3: Dashboard of the WISE-ROP website. The candidate can schedule live video or mentoring sessions with the remote mentor. The event reflects on the calendar of the mentoring team.

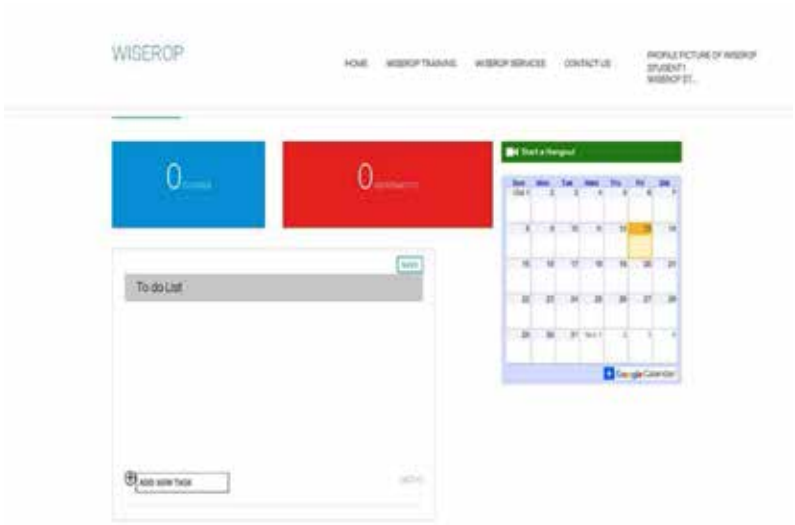

Fig. 4: A screen capture of a live video based mentoring session. Candidates are remotely taught the technique of effective infant retinal imaging (for ROP) with special emphasis on image assessment and reporting.

CONCLUSION

The key aspects of the WISE-ROP program are summarized

- WISE-ROP is a novel, online, live training platform that addresses the scarcity of trained imaging specialists for Retinopathy of Prematurity management especially in underserved and rural centers
- The new gold standard of ROP screening is wide-field imaging. This has replaced the more traditional method of indirect ophthalmoscopy after the medico legal negligence judgment of the Hon, Supreme Court of India, in 2015.
- However, there is a gross deficiency of trained ROP specialists as well as trained and accredited imaging specialists or technicians.
- The KID ROP program has shown how non physicians may be trained to image for ROP in rural centers. The training is validated by the CDC guidelines and has been used in over 100,000 infant imaging sessions
- To train a ROP naïve non-physician to become a level 3 (highest status) imager, over 90 working days in the headquarters were necessary
- With WISE-ROP this is reduced to over 1/10th of the duration of the conventional method
- Besides, WISE-ROP allows training of candidates in their local milieu causing minimal disruption of the routines of these imagers
- WISE-ROP is over 85% less expensive than the conventional regime
- These advantages allow a greater number of non-physicians to be trained in a shorter duration of time.
- The impact of this would be felt as a ten fold increase in the number of trained imagers would lead to a compounding effect across the nation
- The program has also been piloted on international candidates and could be a source of health tourism and e-medicine commerce.
- WISE-ROP is the first online training program for ROP in the world and exploits the decade long program's curriculum which provides theoretical and practical, skill based learning on a novel e-learning platform.

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Low Concentration Atropine (0.01%) To Control The Progression Of Axial Myopia In Children

Dr. Jitendra Nenumal Jethani, Dr. Paaraj Dave

ABSTRACT

Atropine eye drops prevent myopic progression. We did a study to compare the effects of low concentration atropine eye drops (0.01%) with placebo eye drops in children between 5-12 years of age.

All the children taken in the study has history of axial myopic progression. This was a randomised control trial and the subjects were assigned randomly in the case or control group. All the observers were masked to the drops. All investigations were done at 6 months, 1, 2 and 3 years

Atropine eye drops (0.01%) was prepared by diluting it with lubricating eye drops. The difference in axial growth in the atropine user group in right eye was 0.8 and in left eye was 0.7 mm whereas in the control group the axial growth was 1.6 mm in the right eye and in the left eye is 1.8 mm. The axial growth is halved with usage of atropine eye drops 0.01%

INTRODUCTION

Atropine (1%) eye drops is known to prevent progression of myopia.[1] However, practical problems especially photophobia and accommodation loss are some of the important problems which prevents its widespread use. Since atropine (0.01%) eye drops has shown promise in retarding the progression of myopia[2-5] we did a study to compare it with placebo drops to see its effect on progression of myopia

MATERIALS AND METHODS

A total of 60 children were included in the study. The children were randomly assigned to each group depending on the computer generated

chart for randomisation. All the children had a history of myopic progression of at least -0.75/year. All children between 5-12 years were included in the study. The Ethical committee approval was taken from the Institutional Ethical Committee of Dr. Thakorbhai V Patel Eye Institute, Vadodara

The atropine 1% eye drops (Intas Pharma) was mixed with Genteal eye drops (Alcon Lab) and atropine 0.01% eye drops was reconstituted by taking 0.1 ml of Atropine (1%) eye drops and injecting it in 10 ml of Genteal eye drops. The parents were informed to put these drops regularly once a day in the evening.

Cycloplegic refraction, Autorefraction and post mydriatic test with duochrome testing was done for all the children with axial length measurement (Sonomed Inc.) at 1 month, 3 months, 1 year, 2 and 3 year. Children who did not put drops regularly were excluded. Placebo drops of the same lubricant eye drops were provided to the patients. The measurements were done by one of the authors who was masked (SS) and the group was assigned by another author (MT)

All the data was recorded in an excel sheet and was analysed using paired t test.

OBSERVATION

The mean age of the atropine group was 7.2+/- 3.8 years and the control group was 7.2 +/- 5.1 years. The baseline mean spherical equivalent of the spectacle power in atropine group prior to starting the study was -4.5 +/- 3.9 D and in the control group was -4.8 +/- 3.1 D and the baseline axial length in the atropine group was 24.17 +/- 0.9 mm and in the control group was 24.26 +/- 0.8 mm as measured by contact A scan (sonomed Inc.) method

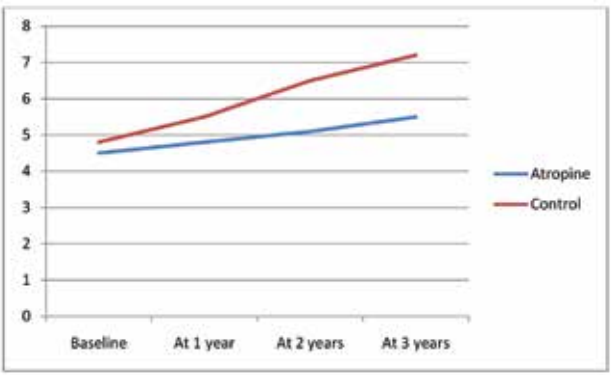

Fig. 1: Shows the increase in the spherical equivalent in the control group and the atropine group

Table 1.

	Baseline		At 1 year		At 2 years		At 3 years	
	Atropine	Control	Atropine	Control	Atropine	Control	Atropine	Control
Axial Length	24.17 +/- 0.8	24.26 +/- 0.9	24.42 +/- 1.1	24.73 +/- 1.2	24.61 +/- 0.9	25.33 +/- 1.3	24.96 +/- 1.1	25.77 +/- 1.6
Spherical Equivalent	-4.5 +/- 3.9	-4.8 +/- 3.1	-4.8 +/- 4.2	-5.5 +/- 3.5	-5.1 +/- 3.8	-6.5 +/- 4.3	-5.5 +/- 4.1	-7.2 +/- 4.6

DISCUSSION

The role of atropine eye drops in preventing the progression of myopia has been established.[1-5] ATOM 2 study by Chia et al has shown the role of low concentration atropine eye drops in Singapore children. Our study was done on the Indian children. The drops were reconstituted as these drops were not available in the Indian market. Several studies with smaller follow ups have also been done showing the role of low concentration atropine in reducing the progression of myopia.

We had a long follow up of 3 years and children of Indian origin. None of the previous study has Indian population. Only Chia et al[5] have a longer follow up and a larger sample size. Our mean progression both in the control and the atropine eye drops was more than reported by Chia at al[1-5] but was similar to reported by Shu Yi et al[7]

Chia et al[1] in their study ATOM 1 reported a mean increase of axial length of 0.38 mm whereas Shu et al[7] reported an increase in axial length of 0.32 mm in one year.

CONCLUSION

Atropine 0.01% eye drops can be reconstituted and is well tolerated. The axial length increase is reduced and the myopic progression is also effectively reduced by using these drops in children between 5-12 years of age

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Comparing Intralesional Propranolol With Oral Propranolol For Treating Periorbital And Eyelid Capillary Hemangiomas

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INTRODUCTION

Capillary haemangiomas are one of the most common benign tumours of infants, presenting within the first year of life with an estimated prevalence in Indian studies of 0.1 to 0.28%[1] About 80% of the haemangiomas are located in the head and neck region.[2] The periocular lesions can range from strawberry nevi to deeper subcutaneous bluish masses with or without post septal extension. A history of prematurity, low birth-weight, placental anomalies and multiple pregnancies is shown to have a higher incidence of infantile haemangiomas.[3,4] They are usually noted at birth, exhibit rapid postnatal growth followed by slow involution, often leading to a complete regression. Most

haemangiomas can be diagnosed on clinical examination. Imaging with ultrasonography or magnetic resonance imaging is helpful to document vessel density, volumetric size and delineate postseptal extent of deep orbital haemangiomas. Regression rate in periorbital capillary haemangiomas has been studied to be 30% by age three and 70% by age seven.[5,6] The growth patterns of superficial (strawberry nevi) and deeper haemangiomas (orbital and subcutaneous) differ as the latter have a later onset and prolonged period of growth compared to strawberry nevi.[7]

Associated ophthalmic complications include mechanical ptosis, astigmatism and anisometropic amblyopia, deprivational amblyopia (visual axis obstruction), disfiguring proptosis, exposure keratopathy, optic nerve compression or lesion necrosis or infection.[7-9] Periocular capillary haemangiomas may occur simultaneously with oral, nasal, subglottic, and paratracheal haemangiomas which may lead to respiratory obstruction and asphyxia.

In absence of these complications, the treatment for capillary haemangiomas is limited to observation for most cases because of the natural course of spontaneous regression. For the complicated cases, various established treatment modalities include medical therapy with glucocorticoids, systemic beta-blockers, immunomodulators, laser ablation, radiation, embolisation or surgical excision. A review by Léauté-Labrèze published in 2017 recommended that most haemangioma lesions did not require therapy. When treatment was indicated oral propranolol was the first line of choice and a minimum period of 6 months of treatment was necessary to give good results.[10]

REVIEW OF LITERATURE

Various studies on capillary haemangiomas have discussed their presentation, clinical course, diagnostic modalities and treatment options. The role of beta blockers for treating capillary haemangiomas was serendipitously discovered by Léauté-Labrèze in 2008 when they observed a dramatic decrease in size of cutaneous capillary haemangiomas in an infant being treated with propranolol for a cardiac indication.[11]

The proposed mechanisms of action for beta blockers include vasoconstriction, suppression of angiogensis through the hypoxia-inducible factor 1a vascular endothelial growth factor (HIF-1a- VEGF)

pathway and induction of apoptosis of the endothelial cells.[12] In addition, propranolol has shown to have inhibitory action on microRNAs responsible for stem cell like property of the endothelial cells lining the haemangioma. While the exact mechanism is unknown, it is likely that a combination of the above effects is responsible for the therapeutic action of beta blockers.[13-15]

Ames et al evaluated the current trends in the medical management of infantile haemangiomas and concluded that since 2008, propranolol has become the first-line therapy, whereas other medical treatments are used less frequently or when propranolol is unsuccessful.[16] Oral propranolol hydrochloride has obtained FDA approval in March 2014 for treatment of proliferating infantile haemangiomas requiring systemic therapy.[17]

These drugs can be administered via systemic (oral), topical and intralesional routes.[18,19] A study done by Hao et al in 2011 in rabbit eyes evaluated the distribution of propranolol in periocular tissues after oral, intravenous and topical administration. They concluded that topical administration can provide increased concentrations of propranolol in the periocular tissues and is superior to systemic administration for the treatment of periocular haemangiomas.[20] Awadein et al comparatively described the use of intralesional propranolol injection and intralesional triamcinolone in periocular capillary haemangiomas. They documented a statistically comparable reduction in the size of haemangioma, astigmatic error, and degree of ptosis in both groups. No adverse effects were reported during or after intralesional propranolol injection.[21]

A randomized control trial of 45 patients by Zaher et al compared the efficacy and safety of topical and intralesional propranolol with oral propranolol. Excellent response (complete resolution) was achieved in 9/15 patients on 2mg/kg/day oral propranolol (60%), 3/15 in patients on topical propranolol 1% ointment twice daily (20%) and 2/15 in weekly 1mg/ml intralesional propranolol (13.3%), (p value: 0.04). As regard to safety, all 3 modalities proved safe with no major side effects. They concluded that further research is needed to help establish clear guidelines and reach best formulations. Topically administered propranolol could be considered in patients at risk of potential side effects from oral administration. However, as intralesional application did not offer any more benefits, it could not be recommended.[19]

A pilot study by Torres-Pradilla et al in 2013 discussed the role of intralesional propranolol in infantile haemangiomas in six patients (ages between 2 to 12 months) with focal (superficial or mixed) lesions that were of cosmetic concern. All patients received one injection of intralesional propranolol 1mg/ml concentration in a dose of 0.2ml/cm, maximum volume of 1 ml. The clinical response was noted at 4 weeks and injection was repeated in 5 patients who showed some response in terms of reduction in size. Only one patient who showed some response (colour change) with the second dose received the third dose. None of the patients showed any systemic side effects. They concluded that overall beneficial role of intralesional propranolol in infantile haemangiomas was guarded. They attributed the failure of intralesional propranolol in their study to erratic absorption, lack of a local deposit after intralesional injection, inappropriately low dose and number of injections and a higher mean age of patients in their study (7.3 months).[22]

Side effects of systemic propranolol have been evaluated in many studies. In a large systematic review of IHs treated with propranolol, Marqueling et al. reported the most common adverse events as changes in sleep (11.4%) and acrocyanosis (5.1%). The incidence of serious adverse events was rare (symptomatic hypotension in 0.4%, hypoglycaemia in 0.3%, and symptomatic bradycardia in 0.08% patients).[23] Likewise, restlessness, sleep disturbances, constipation, and cold extremities were also observed by de Graaf et al. but they concluded that side effects such as symptomatic hypoglycaemia, hypotension, and bronchial hyperreactivity that needed intervention and/or close monitoring were infrequent and not dose-dependent.[24]

Holland et al reviewed a case series of 21 patients who developed hypoglycaemia related to propranolol use.[25] Propranolol is thought to cause hypoglycaemia by inhibiting glycogenolysis, gluconeogenesis and lipolysis, in a non dose dependent mechanism. In addition, beta blockers mask the early sympathetic signs of hypoglycaemia (tachycardia, sweating and palpitations). It is therefore recommended that in patients with reduced calorie intake due to inter-current illness, propranolol should be temporarily discontinued.[26] It is recommended that those with large haemangiomas should be referred to a paediatric cardiologist before commencing propranolol.[27,28]

Regarding intralesional injections, limited literature is available. The most serious and feared complication is central retinal artery occlusion

(CRAO).[29] A paediatric dermatology research workshop in 2005 cautioned regarding the rare risk of inadvertent intravascular/ophthalmic artery embolization with permanent visual loss during administration of intralesional steroids.[30] Bang et al recommended that while administering intralesional corticosteroid, retinal vessels should be examined during and after injection to monitor for central retinal artery occlusion.[18] Though this has been documented with steroid injection, it may be a potential risk with intralesional propranolol also. In their study comparing intralesional propranolol with intralesional triamcinolone, Awadein et al did not report any adverse effects during or after intralesional propranolol injection.[21]

To summarise, oral propranolol is the established first line treatment for infantile haemangiomas. Though rare, systemic side effects can be associated with oral propranolol. Direct drug delivery with possible additional beneficial injection procedure action with intralesional propranolol needs to be investigated. We planned to evaluate intralesional as an alternative to oral and compare efficacy as well as side effects and safety profile. The primary outcome parameters were reduction in surface area of lesion. The change in appearance, color and ptosis and the keratometric astigmatism were also assessed. Patients were monitored for side effects.

MATERIALS AND METHODS

Study Design

Randomized Phase II Clinical Trial

Duration of study

One and a half years

Sample Size

Twenty patients

The trial was approved by the Institute ethics committee of the place of study(Reference number

IESC/T-446/26.08.2015, RT-8/27.11.2015) and has been registered under theClinical Trial Registry of India (CTRI; Registration Number: CTRI/2017/08/009440).

Patient Selection

Twenty consecutive newly diagnosed, treatment naïve cases of periorbital and eyelid capillary haemangiomas attending the centre

were recruited. They were randomized to two groups using a computer generated random number table. The groups were not matched for age or gender. There was no control "observation only" group.

The inclusion and exclusion criteria are enlisted as follows

Inclusion Criteria

Newly diagnosed treatment naïve cases of periocular and eyelid capillary haemangioma whose guardians signed a written informed consent were recruited.

Exclusion Criteria

Patients having intraorbital spread of lesion, complicated lesions with ulceration and necrosis, or previously treated patients were excluded. Patients with a history of systemic illnesses including recurrent breathing problem/asthma; cardiac problems including AV block, CHF, sinus bradycardia, seizures or developmental delay; abnormal finidngs on blood investigations or a failure to obtain cardiology clearance for intervention were excluded from the study. The patients whose guardians didn't sign the consent or were not willing for investigations, treatment or follow up were also excluded.

Baseline evaluation

Clinical history included age of onset and progression of lesion if any. Birth history and details of gestation were also noted. Systemic evaluation including general physical examination, cardiovascular, respiratory system and per abdomen examination was done. Pre – interventional investigations at the time of enrolment included clinical documentation of size, colour and appearance of lesion. Any associated complications like ptosis, strabismus or other changes were recorded. The fixation preference and dilated retinoscopy of all patients was performed prior to intervention. Visual acuity was also recorded whenever possible. The corneal astigmatism was recorded using a hand held auto refractometer (Retinomax 3+ (Rmax); Nikon Inc., Japan).

Imaging of the lesions was done using orbital ultrasonography and magnetic resonance imaging (MRI) scan of head and orbit. Abdominal ultrasonography, when indicated, was done to document any visceral haemangiomas. Preoperative haemoglobin, bleeding time, clotting time, random blood sugar, liver and kidney function tests were tested when required.

Photographs of the lesions were taken at baseline and on subsequent follow up.

Study Groups

1 Study Group A

10 patients received oral propranolol in a dose of 1 mg/kg/day in two divided doses on day 1 and 2; then 2 mg/kg/day in two divided doses on day 3 and 4 and then 3 mg/kg/day in two divided doses, continued till six months. At the end of six months, the dose was tapered over a period of 6 days and then stopped. Final evaluation was done at 6 months.

2) Study Group B

10 patients received intralesional propranolol in the form of a single injection with a 26 gauge needle. The propranolol used was prepared in strength of 1mg/ml concentration and was provided by the hospital pharmacy of the place of study. The dose for intralesional propranolol was 0.2 ml (of 1 mg/ml concentration) per cm of the greatest linear dimension (GLD) of lesion with the maximum injected dose being 1ml. Injection was administered under general anaesthesia in the operation theatre with monitoring of heart rate and blood pressure. All patients received three injections - at baseline, between 4 to 6 weeks and between 8 to 12 weeks. Follow up was continued and final evaluation was done at 6 months.

The two groups of patients were admitted and underwent cardiovascular and respiratory monitoring for the first 48 hours after treatment. Heart rate, blood pressure and respiratory system were also examined on subsequent follow up visits done at week 1, 2, 4, 6, 8, 12 and then at 4 months and 6 months.

Observation Parameters

Efficacy of therapy was measured as

1. Regression in size on clinical examination

   a. Percentage decrease in area (length along longest linear dimension and width perpendicular to the longest linear dimension; measured clinically using digital callipers)

   b. Grading for reduction in area on the basis of the following scale (modified and adapted from the study done by Awadein et al).[21]

Table 1. Grading scale for percentage area reduction	
Excellent	>90%
Very good	70-89.9%
Good	50-69.9%
Fair	30-49.9%
Poor	<30%

2. Reduction in degree of ptosis
   a. Mild Ptosis: <2 mm
   b. Moderate Ptosis: 2-4 mm
   c. Severe Ptosis: >4 mm
3. Regression in colour (from dark red to pale pink)
4. Regression in appearance (from elevated to flat)
5. Change in astigmatism
6. Side effects

Systemic side effects including cold extremities, change in feeding habits, constipation, gastric reflux or regurgitation, history of jitteriness or lethargy were noted. Other symptoms evaluated were wheezing, bradycardia or hypoglycaemia. Local side effects like necrosis or ulceration at lesion site were documented. Any other side effects as reported by guardians or noted on evaluation during follow up were also noted.

Analysis of Study

Data was recorded in a predesigned proforma and Excel spreadsheet. Categorical variables were summarised as frequencies. Quantitative variables were summarised as mean ± SD or median if non-normally distributed. Quantitative data results were compared and interpreted using the two-sided students t test with an alpha error of 5% and a power of 80%. A p value of ≤ 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics in groups 1 and 2

Twenty patients were recruited after taking written informed consent from the guardians. They were divided into 2 groups on the basis of random number tables with 10 patients in group 1 (oral propranolol,

case 1 to case 10) and 10 patients in group 2 (intralesional propranolol, case 11 to case 20). The baseline characteristics were analysed and were statistically comparable except for gender. These are summarized below.

Table 2. Summary of baseline characteristics in groups 1 and 2

Demographics	Group 1	Group 2	p value
Age (median)	8 months	10 months	0.107
Gender	7 female, 3 male	2 female, 8 male	0.02
Birth complications			0.785
Uncomplicated	8	7	
Breech	1	1	
Twins	1	1	
Low birth weight	0	1	
Period of gestation			0.531
Term	9	8	
Preterm	1	2	
Type of birth		0.606	
Normal vaginal delivery	8	7	
Caesarean Section	2	3	
Type of lesion		0.475	
Skin surface localized	1	4	
Skin surface extensive	1	1	
Conjunctival localized	3	2	
Deep extensive	5	3	
Area (median)	331.53 mm2	257.62 mm2	0.205
Colour		0.549	
Dark red-blue	7	7	
Red	2	3	
Pink	1	0	
Same as surrounding skin	0	0	
Appearance		0.08	
Elevated	7	9	
Mildly elevated	3	1	
Flat	0	0	
Ptosis		0.98	
None	4	2	
Mild<2mm	0	1	
Moderate 2-4mm	1	4	
Severe>4mm	2	3	
Astigmatism	-2.8588 D at 179.8 degrees	1.617 D at 90.16 degrees	0.502

REPRESENTATIVE IMAGES

a) Type of lesion

Skin surface localized: 25%	Skin surface (multiple) extensive: 10%	Conjunctival surface localized: 25%	Deep with soft tissue extension: 40%
			
Case 15	Case 4	Case 7	Case 6

Fig. 1: Representative images for clinical types (as described above)

b) Colour

Dark Red-Blue (baseline)	Red (baseline)	Pink (6 months)	Same as surrou-nding structure (6 months)
			
Case 17	Case 14	Case 12	Case 10

Fig. 2: Representative images for colour categories (as described above)

c) Appearance

Elevated (baseline)	Mildly elevated (baseline)	Reduced (6 months)	Flat (6 months)
			
Case 11	Case 16	Case 14	Case 5

Fig. 3: Representative images for appearance categories (as described above)

d) Ptosis

Mild ptosis < 2 mm	Moderate Ptosis 2-4 mm	Severe ptosis >4mm
		
(Case 18)	(Case 1)	(Case 2)

Fig. 4: Representative images of amount of ptosis as described above

OUTCOME

a) Change in area of lesion

All ten patients in the group 1 (oral propranolol group) showed a significant response to treatment. The average percentage area reduction was 83.48% ±11.67% at the end of six months. (p value 0.0019). A similar response was seen in all ten patients in group 2 who received 3 intralesional injections of propranolol at 4-6 week intervals. At 6 months, the average percentage area reduction was 67.78% ± 21.71% (p value 0.0019).

Table 3. Change in area of lesion from baseline to 6 months in groups 1 and 2

	Group 1 n=10	Group 2 n=10
Size of lesion (area) at baseline (mean +/- SD)	615.77 +/- 592.67 mm2	332.3 +/- 261.94 mm2
Size of lesion (area) at 6 months (mean +/- SD)	130.34 +/- 162.86 mm2	132.89 +/- 149.76 mm2
Average percentage area reduction (mean +/- SD)	83.48% +/- 11.67	67.78% +/- 21.71
p value	0.0019	0.0019
p value group 1 vs. group 2	0.056 (t test)	

The patients in group 1 who received oral propranolol showed an overall greater percentage reduction in area with treatment as compared to the patients in group 2 who received the intralesional injection. This difference in percentage reduction in area was significant by statistical analysis at 4 months (p value 0.047). However, this difference was not noted at the 6 month follow up (p value 0.056). Thus, intralesional propranolol seemed comparable to oral propranolol therapy at the 6 month analysis.

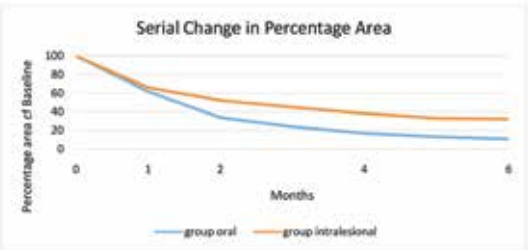

Fig. 5: Serial reduction in percentage area in groups 1 and 2

The percentage reduction values were further divided into categories in order to grade the response as excellent, very good, good, fair and poor.

Table 4. Percentage reduction in area size according to grading scale in groups 1 and 2

Grade	Reduction in area% at 6 months	Group 1	Group 2
Excellent	>90%	4	3
Very good	70-89%	4	2
Good	50-69%	2	3
Fair	30-49%	0	2
Poor	<30%	0	0
p value (Fishers exact test)0.56			

Forty per cent of the patients in group 1 showed an excellent response as compared to 30% in group 2. All ten patients in group 1 had more than 65% improvement in area and the response was good or higher. As compared to this, only 80% of the patients in group 2 had a good or higher response. Twenty per cent patients in group 2 had a fair response with the least responsive patient showing only 31.48% reduction in area. Thus, even though there was a better response in group 1 as compared to group 2, this was not significant statistically. (p value 0.56). The averagearea at baseline and on follow up at 1,2,4 and 6 months in each group is summarised in table 5.

Table 5. Summary of area at baseline and on follow up

Time point	Group 1 Average area in mm2	Group 2 Average area in mm2
Baseline	615.77	332.3
1 month	415.2	251.12
2 months	276.75	202.12
4 months	160.15	151.5
6 months	130.34	132.89

b) Astigmatism

The keratometry was done with the help of hand held auto kerato-refractometer and the amount of corneal astigmatism in the affected eye was noted at baseline and at six months. The change in astigmatism after treatment in each group was compared as vectors.[31] This was

done by calculating the mean preoperative and postoperative centroids, as described by Holladay et al.[32] Briefly, polar values were converted to Cartesian values using the following equations:

x = cylinder × cos (2 × axis) andy = cylinder × sin (2 × axis)

In the formulas, the angle of the axis of astigmatism is doubled to give the correct x and y values. The centroid, or mean of a set of x and y values, was calculated by independently finding the mean of each variable (xm, ym). The centroid (mean astigmatism) was then converted back to standard polar notation as follows:

Cylinder = (xm2 + ym2) 0:5 and Angle = 1/2 arc tan (ym / xm)

(If xm and ym > 0, then axis = angle; if xm < 0, then axis = angle + 90 degrees; if xm > 0 and ym < 0, then axis = angle + 180 degrees).

The table represents the amount of astigmatism in dioptres at the steep axis, along with the axis at baseline and at 6 months in all 20 patients.

Table 6. Astigmatism (steep axis Dioptre and degrees) at baseline and 6 months

	Baseline (amount in D)	Baseline (axis in degrees)	6 months (amount in D)	6 months axis in (degrees)	p value
Group 1	2.86	179.8	1.13	179.8	0.0045
Group 2	1.62	90.2	0.75	179.9	0.0001

The astigmatism analysis was done using the method described by Holladay, detailed above. Both groups showed a significant amount of reduction in mean dioptres of astigmatism. There was a 60.53% reduction in amount of astigmatism in group 1 (p value 0.0045) and a 53.54% reduction in amount of astigmatism in group 2 (p value 0.0001). On comparing the amount of reduction in dioptres of astigmatism between the two groups, there was no significant difference; p value 0.49.

c) Change in colour

In group 1, 70% had a dark red-blue colour at baseline. At the end of 6 months, 80% had colour same as surrounding structure and 20% had a pink appearing lesion showing a significant improvement (p value 0.0404).

In group 2, 70% patients had a dark red-blue colour at baseline and 30% had red appearing lesions. At the end of 6 months, 20% patients

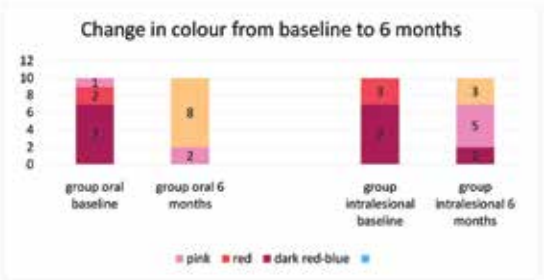

Fig. 6: Graph depicting change in colour from baseline to 6 months

remained to have a dark red-blue colour and 50% had a pink appearing lesion. Only 30% patients had a colour that was same as the surrounding skin. This change in colour was statistically significant within group 2 (p value 0.02). The overall improvement in colour was better in group 1 than group 2 with 80% patients having colour same as surrounding structure at the end of 6 months, compared to only 30% in group 2 having the colour same as surrounding structure.

d) Change in Appearance

The change in appearance in terms of elevation of lesion was also documented. Appearance categories were defined subjectively as grade 2 if significantly elevated, mild elevation/ reduction from baseline but not flat as grade 1 and flat as grade 0. At baseline, 70% patients in group 1 had lesions that were significantly elevated. Three patients had mild elevation and were graded as grade 1. At the end of 6 months, all patients' lesions showed reduction in elevation with 60% patients having flat appearance. (p value 0.0186).

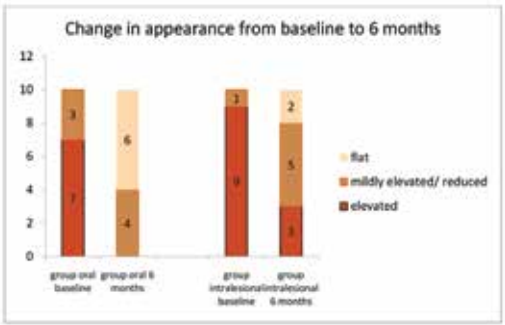

Fig. 7: **Graph depicting change in appearance from baseline to 6 months**

In group 2, at baseline 90% had elevated and one patient had mildly elevated appearance. At the end of 6 months, 30% patients still had a significantly elevated lesion and another 50% showed some reduction but persistent elevation. Only 20% patients had a flat lesion. The reduction in elevation after treatment in group 2 was not statistically significant. (p value 0.0719).

e) Change in Ptosis

There was improvement in ptosis in both the groups from baseline to 6 months. At baseline, four out of six patients in group 1 had moderate ptosis and 2 had severe ptosis. At the end of 6 months three had mild ptosis of less than 2 mm and 3 had moderate ptosis. Average percentage reduction in ptosis was 66.11 ± 14.21% in group 1.

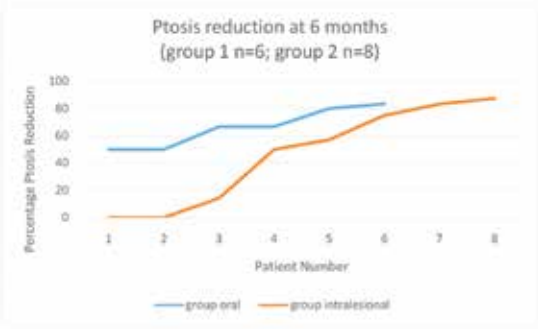

Fig. 8: Graph depicting improvement in ptosis from baseline to 6 months

In group 2, three patients had severe ptosis at baseline, 4 had moderate and 1 had mild ptosis. At the end of six months, 2 patients continued to have severe ptosis, 1 had moderate ptosis and 5 had mild residual ptosis of less than 2 mm. The average percentage reduction in ptosis was 45.91 ± 36.52%. Two cases did not show any improvement in ptosis (percentage change at 6 months = 0%)

There was a better percentage reduction in group 1 as compared to group 2 even though the reduction was not statistically significant. All six patients with ptosis in group 1 showed improvement. As compared to this, two patients out of eight in group 2 did not show any improvement in the amount of ptosis.

f) Side effects of treatment

The parents were asked for presence of any side effects like lethargy, poor feeding, gastric reflux/regurgitation, wheezing or irritability. Heart rate and capillary filling time were assessed at serial follow up. Specific local side effects like local ulceration or necrosis at side of haemangioma were noted. Out of group 1 (oral propranolol) 70% patients didn't report any side effects. 20% patients noted lethargy and 10% (1 patient) noted poor feeding during the follow up period. The parents were asked to monitor the child more frequently and alter timing of evening dose of propranolol closer to bedtime. The dose was not reduced in the group and the treatment was continued as per protocol. None of the patients in group 2 (intralesional propranolol)

reported any side effects, local or systemic. This difference was not statistically significant (p value 0.171).

g) Retrospective subgroup analysis within Group 2

Within group 2 (those receiving intralesional propranolol), we retrospectively compared the baseline characteristics of the patients having excellent or very good response with an area reduction >70% at 6 months (group 2a, n=5) with the remaining patients who showed a lesser response (group 2b, n=5).

The data is summarized in the table below.

Table 7. Comparison within subgroups 2a and 2b

Parameter	Group 2a (n=5)	Group 2b (n=5)	p value
Age (mean; median)	10,8	26.2,21	0.1662
Type (nature) of lesion	N=5	N=5	0.524
Area baseline (mean ±SD)	171.07 ±106.26 mm2	493.536 ±308.6 mm2	0.049
Colour	N=5	N=5	0.167
Appearance	N=5	N=5	0.9

The only statistically significantly different parameter between these two groups was area at baseline. The lesions, which showed an excellent or very good response, had a smaller size at baseline. The overall percentage area reduction in this group (group 2a) was 85.28% (range 72.65% to 92.31%). As compared to this, the overall percentage reduction in area in group 2b was 50.28% (range 31.48% to 69.1%). This difference in these two groups was statistically significant with a p value of 0.0018. Thus, small, localized lesions showed significantly better response to intralesional propranolol.

DISCUSSION

Capillary haemangiomas are one of the most common infantile benign tumours with a reported prevalence of 0.1-0.28% in Indian studies.[1,33]

These benign tumours are usually noted at birth, exhibit rapid postnatal growth followed by slow involution, often leading to a complete regression. Regression rate in periorbital capillary haemangiomas has been studied to be 30% by age three and 70% by age seven.[6]

Probable risk factors shown in various studies include a history of female gender, prematurity, low birth-weight, placental anomalies and multiple pregnancies.[3,4]

In the present study, 55% patients were male and 45% were female. Their ages ranged from 3 months to 5 years (60 months). The median age was 8 months (range 3-12 months) in group 1 (oral) and 10 months (range 5-60 months) in group 2 (intralesional). Three patients had history of preterm delivery and two of them had history of twin pregnancy. Majority had history of normal vaginal delivery (15 patients). One patient had a history of low birth weight. Thus, the findings of low birth weight, history of preterm delivery and twinning were seen in some patients in the present study group. However, in the absence of a control cohort, we are unable to comment on the causative significance of these findings.

Haemangiomas can be classified as superficial, deep, or compound. The superficial lesions include red nodules without a subcutaneous component. A deep haemangioma protrudes with an overlying bluish tint or telangiectasia. Compound haemangiomas are lesions having both deep and superficial components.[34] In the present study, we classified the periorbital lesions into four main types: skin surface localized, skin surface extensive, conjunctival surface localized and deep orbital lesions. This distribution was based on clinical and MRI findings. Majority had deep extensive lesions (40%); 25% had skin surface localized lesions, 25% had conjunctival localized and another 10% had skin surface extensive lesions. The overall distribution was 12 patients with superficial lesions, 5 with deep lesions and 3 with compound lesions.

Lesions of the head and neck region often coincide with the distribution of the trigeminal nerve. Multifocal haemangiomas also exist, and infants with greater than 5 lesions should undergo workup to rule out visceral involvement.[34] We also observed the distribution of lesions and noted the site of each lesion in case a patient had more than one lesion or extensive involvement. Three patients also had associated cutaneous lesions outside the head and neck region. Where warranted, patients underwent an abdominal sonography in consultation with the paediatrician. None of the twenty patients in the present study showed any visceral lesions.

Most frequently, the lids were involved with 10 patients having an upper lid involvement and 4 patients having a lower lid involvement. Eight patients had a deep component with orbital involvement. Five patients had involvement of the eyebrow skin, 3 had lesions involving the forehead and nasal bridge and another 2 had involvement of the upper lip and cheek.

RESPONSE TO TREATMENT

Treatment of haemangiomas has known to lead to a reduction in size as well as change in colour and appearance. Léauté-Labrèze reported that treatment with propranolol causes vasoconstriction of supplying capillaries. This reduces the blood flow within the haemangioma producing a visible change in colour and a palpable softening of the haemangioma. These effects can be observed within 1–3 days after the onset of therapy.[11]

In a review article by Tavakoli et al in 2017, the colour of periocular haemangiomas was described. Superficial lesions appearing at birth or after a few months comprised of a red papule or nodule having a flat or a rough surface and blanching with pressure. Deep lesions caused blue to purple discoloration of the skin, or may only caused anatomical disfigurement without discoloration.[35] Various case reports of treatment of periocular haemangiomas with propranolol have reported a similar reduction in colour from dark red to pale pink and resolution of telengiaectatic surface vessels. In addition to this, with reduction in size there was also flattening and change in appearance of the lesions.[36-39]

A meta-analysis comparing propranolol and other treatments (steroids, laser ablation, surgery, atenolol and timolol) for infantile haemangiomas by Liu et al reported greater efficacy and better safety profile of propranolol as compared to the other modalities.[40]

In the present study, we characterized the baseline features of the lesions in terms of surface area, colour and appearance of lesion and presence of dilated vessels. These features were subsequently evaluated at 6 months to assess the response of the lesion to the respective treatment.

Oral propranolol is highly efficacious in cutaneous infantile haemangiomas with a reported response rate of 98% (range 82-100%) as shown in a review by Marqueling et al. They reviewed 41 articles with over 1200 patients of IH receiving oral propranolol. The response rate was defined as any improvement with oral propranolol. Treatment response rates were comparable for studies evaluating IHs at specific sites, such as periorbital IHs.[23]

Qin et al performed one of the largest studies on oral propranolol in 58 infants with infantile haemangiomas. They administered oral propranolol at a dose of 1–1.5 mg/kg/day and reported a response rate of "good to excellent" in 67% of patients.[41]

Various studies have reported high efficacy of oral propranolol in periorbital haemangiomas.[37,39,42-48] These are summarized in table 8.

Table 8. Summary of various studies on oral propranolol in periorbital capillary haemangiomas

Author	Demographics	Dose of oral propranolol	Outcome
Sans et al[37] 2009	Number of cases: 13 (total 32, 13 periocular) Age at enrolment: 2-41 months Duration: 3-10 months	2-3mg/kg/day	The efficacy of propranolol reached 100%, with the first effects appearing in the first hours with change in colour and softening of lesion USG at 60 days showed mean regression of 40% in 11 patients
Li et al[42] 2010	Number of cases: 4 Age at enrolment: 11 weeks-2.5 years Duration: 6-12 months	2mg/kg/day	Reduction in lesion on imaging, improvement in proptosis and astigmatism in all patients.
Haider et al[44] 2010	Number of cases: 17 Age at enrolment: 3 weeks to 12 months Duration: until resolution / 9-11 months of age	Initially 0.5, increased slowly to 2mg/kg/day	10 excellent responders >50% reduction to near total resolution 6 good response moderate decrease in size 1 fair response no additional growth but no clinically significant regression
Cheng et al[45] 2010	Number of cases: 10 area: 543.2 mm^2 Age at enrolment: 3-11 months Duration of treatment: 12-42 weeks	2mg/kg/day	Mean pre treatment area: 756.7 mm^2; Mean post treatment (p value 0.075) Mean pre treatment astigmatism 2.8D Mean post treatment astigmatism 1.9D
Claer-hout et al[39] 2011	Number of cases: 10 Age at enrolment: 2-19 months Duration: 7.6 months mean duration	2mg/kg/day	5 excellent responders >50% reduction to near total resolution 3 good response moderate decrease in size 2 fair response no additional growth but no clinically significant regression
Hari-krishna et al[46] 2011	Number of cases: 4 Age at enrolment: 3-19 months Duration: more than 6 months	2mg/kg/day	Notable regression in the deeper orbital components was observed on examination and imaging in all subjects

Missoi et al[47]	Number of cases: 17 Age at enrolment: 2.2-5.6 months (IQR) Duration: 4.1-7.2 months (IQR)	2mg/kg/day	Median change in the surface area was 61% (interquartile range, 32%-64%) of the original size
Snir et al[43] 2011	Number of cases: 30 Age at enrolment: 1 to 17 months Duration: 1-15 months	2mg/kg/day	The findings revealed a mean diseased periorbital area of 12.7±21.7 cm^2 before therapy and 6.0±9.5 cm^2 after therapy, with a reduction of >50% There were non-significant reductions of 31% in spherical power and 28% in mean spherical equivalent
Léauté-Labrèze et al[48] 2015	Number of cases: 318 (Total 456, 318 facial) Age at enrolment: 35-105 days Duration: analysis at 24 weeks	Out of 318: a) 40 patients placebo b) 71 patients 1mg/kg/day for 3 months c) 72 patients 1mk/kg/day for 6 months d) 64 patients: 3mg/kg/day for 3 months e) 71 patients 3mg/kg/day for 6 months	Nearly complete resolution was defined as a minimal degree of telangiectasia, erythema, skin thickening, soft-tissue swelling, and distortion of anatomical land- marks. Overall, 61 of 101 patients (60%) assigned to the selected propranolol regimen and 2 of 55 patients (4%) assigned to placebo had successful treatment at week 24 (P<0.001)
The present study	Number of cases: 10 Age at enrolment: 3-12 months Duration: 6 months	3mg/kg/day	All 10 patients had more than 65% reduction in area percentage In addition, there was improvement in colour and appearance, reduction in ptosis and astigmatism

A similar efficacy with oral propranolol was also observed in the present study. All patients in group 1 (n=10) receiving oral propranolol showed a significant response to treatment with an average percentage area reduction of 83.48% ±11.67% at the end of six months (p value 0.0019). All ten patients had more than 65% improvement in area and the response was graded as good or higher. In addition to reduction in area, there was improvement in colour and appearance of the lesions. 70% had a dark red-blue colour at baseline. At the end of 6 months, 80% had colour same as surrounding structure and 20% had a pink appearing lesion showing a significant improvement. At baseline, 70% patients in group 1 had lesions that were significantly elevated and three patients had mild elevation. At the end of 6 months, all patients' lesions showed reduction in elevation with 60% patients having flat appearance. Dilated vessels seen at baseline in 4 out of the 10 patients became normal appearing in 3 patients at the end of 6 months.

Only a few studies are available which discuss the role of intralesional propranolol in periocular haemangiomas. Awadein et al compared intralesional steroid with intralesional propranolol injection in periocular capillary haemangiomas. They administered a single injection of intralesional propranolol 1 mg/ml concentration in a dose of 0.2 ml/cm greatest linear dimension (GLD) with maximum dose of 1 ml in twelve cases. Final assessment was done at 4 months. Regression was noted in 10 out of 12 patients in terms of reduction in size, flattening of lesion and blanching of colour. At the end of the follow-up period, 42% of patients showed an excellent response with almost complete resolution of the lesion, 25% showed a good response with more than 50% reduction in the size of the lesion and 17% showed a fair response with less than 50% reduction in the size of the lesion. Only two patients (17%) were resistant to treatment. The intralesional steroid group showed regression in eight out of 10 patients with 40% patients showing an excellent response. The onset of regression was delayed in the steroid group as compared to the propranolol group.[21]

Zaher et al compared oral, topical and intralesional propranolol for problematic haemangiomas. In their study, an excellent response (complete resolution) was achieved in 9/15 patients with oral propranolol (60%), 3/15 with topical propranolol (20%) and 2/15 with intralesional propranolol (13.3%). The onset of initial response and the time taken for final response was longer in the intralesional group. As intralesional application did not offer any benefit over topical application and

oral propranolol, it could not be recommended.[19] Torres-Pradilla et al studied the role of intralesional propranolol in six patients with facial capillary haemangiomas. They concluded that overall beneficial role of intralesional propranolol in infantile haemangiomas was guarded. They attributed the failure of intralesional propranolol in their study to erratic absorption, lack of a local deposit after intralesional injection, inappropriately low dose and number of injections and a higher mean age of patients in their study (7.3 months).[22]

In the present study, the response to treatment with intralesional propranolol was assessed in ten patients in group 2. At 6 months, the average percentage area reduction was 67.78% ± 21.71% (p value 0.0019). 80% of the patients in group 2 had a good or higher response (>50% reduction in area percentage). Twenty percent patients in group 2 had a fair response (30-49.9% reduction) with the least responsive patient showing only 31.48% reduction in area. 70% patients had a dark red-blue colour at baseline and 30% had red appearing lesions. At the end of 6 months, 20% patients remained to have a dark red-blue colour and 50% had a pink appearing lesion. Only 30% patients had a colour that was same as the surrounding skin. In group 2, at baseline 90% had elevated and one patient had a mildly elevated appearance. At the end of 6 months, 30% patients still had a significantly elevated lesion and another 50% showed some reduction but persistent elevation. Only 20% patients had a flat lesion. Out of the five patients with dilated vessels at baseline in group 2, three had normal appearing vessels at the end of 6 months.The results seen in the present study in patients receiving intralesional propranolol are significantly better than those reported by Torres-Pradilla et al and Zaher et al. These are summarized in Table 9.

A further analysis in comparing the reduction in percentage area between groups 1 and 2 in the present study revealed no statistically significant difference in response between oral and intralesional propranolol at 6 months (p value 0.056). Thus, intralesional propranolol seemed comparable to oral propranolol therapy at the six months analysis in the present study.

Associated Complications

Although most infantile haemangiomas are usually not problematic, upto 12% can cause significant morbidity, including disfigurement, difficulty in feeding, ulceration, vision loss, airway compromise, congestive heart failure, and death.[9, 49-53]

Table 9: Summary of various studies on intralesional propranolol in capillary haemangiomas			
Author	Demographics	Dose of propranolol	Outcome
Awade-inet al[21] 2011	Number of cases: 12 for intralesional propranolol 10 for intralesional triamcinolone Age at enrolment: Propranolol: 5.9 ±2.7 months Triamcinolone: 6.1±2.9 months Duration: 4 months follow up	Propranolol 1mg/ml Triamcinolone 40mg/ml Single injection 0.2ml/cm GLD, maximum of 1 ml	Propranolol group: Pre treatment size: 8.1 ±3.4, range 3.6–14.3 cm2; Post treatment size: 3.6 ±2.6, range 0– 7.1 cm2; 10/12 showed regression Steroid group: Pre treatment size: 7.9 ±3.6, range 3.5–14.1 cm2; Post treatment size:3.7 ±2.5, range 0–7.5 cm2; 8/10 showed regression
Torres-Pradilla et al[22] 2013	Number of cases: 6 Age at enrolment: 7.3±4.3 months Duration: 7.3 months	1mg/ml, 0.2ml/cm of GLD Injection repeated if response seen at 1 month; 1 patient: 1 injection; 4 patients: 2 injections; 1 patient: 3 injections	No significant response in terms of regression in size, colour or appearance
Zaher et al[19] 2013	Number of cases: 45 (15 in each group) Age at enrolment: Group A: 3-18 months Group B: 1-18 months Group C: 3-18 months Duration: Group A: 3-9 months Group B: 5-10 months Group C: 5-12 months Analysis at 6 months after completing treatment	Group A: oral propranolol 2mg/kg/day Group B: topical propranolol 1% ointment Group C: intralesional propranolol 1mg/ml 0.2ml/GLD weekly injections	Improvement noted in 86.7% patients in group A, 66.7% patients in group B and 53.3% patients in group C Recommendations: First line of treatment of IH is oral propranolol. Topical propranolol could be considered in patients at risk of potential side effects from oral administration. No benefit with intralesional propranolol hence not recommended.
The present study	Number of cases: 10 Age at enrolment: 5-60 months Duration of follow up: 6 months	1mg/ml propranolol hydrochloride 0.2ml/cm of longest linear dimension (maximum of 1 ml) 3 injections 4-6 weeks apart	An average area reduction of 67.78±21.71% (p value 0.0019) 8 out of 10 had >50% reduction in size In addition, there was improvement in colour and appearance, reduction in ptosis and astigmatism

A study focusing on periocular haemangiomas done by Haik et al reported that complications could occur in up to 80% of untreated or, alternatively, treatment-resistant periocular capillary haemangioma cases.[54] Even though most lesions regress spontaneously, treatment is however indicated if there is an obstruction of the visual axis, induced astigmatism, strabismus, exposure keratitis, rapid growth, optic nerve compression, severe ptosis or poor cosmesis.[51,55-59] Amblyopia is the primary concern because of stimulus deprivation, induced anisometropia (mainly oblique astigmatism), secondary strabismus, or globe displacement.[60]

Anisometropia induced amblyopia, the most significant sequelae in terms of frequency, affects up to 60% of these patients.[8,54] This form of amblyopia is usually the result of mass-induced indentation on the infant's flexible sclera and cornea, causing distortion and astigmatism.[9,51] Deprivation amblyopia resulting from obstruction of the visual axis by the lesion is an additional potential cause for amblyopia. A study on refractive and structural changes of periorbital haemangiomas by Snir et al reported the association of anisometropic astigmatism, refractive amblyopia and ptosis - induced amblyopia in periocular haemangiomas. They treated 30 patients with oral propranolol 2 mg/kg/day for a mean duration of 7.3±3.5 months. They reported a reduction of 40.5% in mean cylindrical power in the involved eye after treatment compared with baseline (p value 0.02). There was a non-significant reduction of 31% in spherical power (p value 0.13), and a non-significant decrease of 28% in mean spherical equivalent (p value 0.1). In their study, in addition to oral propranolol, patients with significant refractive anisometropia (mainly astigmatism) or partial occlusion of the visual axis were prescribed glasses; those older than 4 months (3 patients) were also given anti amblyopia treatment (patching).[43]

In a study by Fabian et al, the role of oral propranolol 2 mg/kg/day for the reduction of astigmatism was assessed in three cases of periocular haemangiomas. The mean astigmatic error decreased from 2.83 Dioptres (range 2.5-3.0 D) before propranolol treatment to 1.33 dioptres (range 1.0-2.0 D) after 1 month of treatment. A rapid therapeutic effect was noticed in all cases, including a change in lesion size and colour.[60] Herlihy et al studied the effect of oral propranolol treatment on visual acuity and astigmatism in 17 patients of periocular haemangiomas. Mean astigmatism in affected eyes was 1.90 D pre-treatment and 1.00 D post-treatment (p value 0.0033), and 0.69 D and

0.40 D, respectively, in unaffected eyes (p value 0.19). Patients showed a monophasic reduction in astigmatism over 12 months. None of the patients had visual acuity in the affected eye more than 1 standard deviation below the age - matched norm. No patient experienced significant side effects when treated with oral propranolol.[61]

In the present study, keratometry was recorded in all patients and where possible, visual acuity was also documented. Analysis of corneal astigmatism was done at baseline and at 6 months. The mean pre treatment corneal astigmatism in group 1 was 2.86 D at 179.8 degrees. There was a 60.53% reduction in amount of astigmatism and mean post treatment astigmatism was 1.13 D at 179.81 degrees; p value 0.0045. The mean pre treatment astigmatism in group 2 was 1.62 D at 90.16 degrees. There was a 53.54% reduction in amount of astigmatism and mean post treatment astigmatism was 0.75 D at 179.87 degrees; p value 0.0001. On comparing the amount of reduction in dioptres of astigmatism between the two groups, there was no significant difference; p value 0.49. Thus both groups showed a significant reduction in astigmatism with treatment and the reduction was comparable between the two treatment groups.

Regression in size of lesion results in improvement of ptosis especially for upper eyelid lesions. Severe ptosis is one of the indications for treating periocular haemangiomas. Harikrishna et al have studied the effect of oral propranolol and reduction of ptosis from baseline in four patients.[46] In the present study, fourteen out of 20 patients had some degree of ptosis at baseline. At baseline, four out of six patients in group 1 had moderate ptosis (2-4 mm) and 2 had severe ptosis (>4 mm). At the end of 6 months three had mild ptosis of less than 2 mm and 3 had moderate ptosis. Average percentage reduction in ptosis was 66.11 ±14.21% in group 1. In group 2, three patients had severe ptosis at baseline, 4 had moderate and 1 had mild ptosis. At the end of six months, 2 patients continued to have severe ptosis, 1 had moderate ptosis and 5 had mild residual ptosis of less than 2 mm. The average percentage reduction in ptosis was 45.91 ±36.52%. Two cases in group 2 did not show any improvement in ptosis. The reduction in ptosis was as a result in reduction in overall size of the lesion. Other complications assessed in the present study were squint (none), presence of ulceration or necrosis (none) and systemic evaluation and presence of any cardiorespiratory or abdominal complications (none).

Side Effects of Therapy

Side effects of systemic propranolol have been evaluated in many studies. Propranolol is thought to cause hypoglycaemia by inhibiting glycogenolysis, gluconeogenesis and lipolysis. Children seem to be more susceptible to hypoglycaemia as they have lower glycogen stores leading to a reduced fasting ability and a higher glucose utilisation rate. In addition, beta blockers mask the early sympathetic signs of hypoglycaemia like tachycardia, sweating and palpitations. In a large systematic review of IHs treated with propranolol, Marqueling et al. reported the most common adverse events as changes in sleep and acrocyanosis seen in 11.4% and 5.1% patients and rare incidence of serious adverse events such as symptomatic hypotension in 0.4%, hypoglycaemia in 0.3%, and symptomatic bradycardia in 0.08% patients, respectively.[23] In a review on oral propranolol by Cornish et al in 2011, adverse effects with propranolol for infantile periocular capillary haemangiomas were documented in 26 of the 100 cases. However, most of these were not serious enough to warrant stopping or amending the dose of propranolol; propranolol was only discontinued in five cases.[62]A meta-analysis comparing propranolol and other treatments (steroids, laser ablation, surgery, atenolol and timolol) for infantile haemangiomas by Liu et al reported greater efficacy and better safety profile of propranolol as compared to the other modalities. Their review included 61 studies in which 30 studies with a total of 1893 patients were based on oral propranolol. Out of these 1893 patients, side effects were reported in 286 (15.11%) patients only. These included insomnia, hypotension, respiratory disorder, diarrhoea, cold extremities, fatigue, hypoglycaemia, constipation, and other gastrointestinal disturbances.[40] Various studies have reported side effects with use of oral propranolol for treatment of capillary haemangiomas.[37,39,42-48] These are summarized in table 10.

In the present study, in group 1 70% patients didn't report any side effects. 20% patients noted lethargy and 10% (1 patient) noted poor feeding during the follow up period. The parents were asked to monitor the child more frequently and alter timing of evening dose of propranolol closer to bedtime. The dose was not reduced in the group and the treatment was continued as per protocol.

A research workshop in 2005 on paediatric dermatology discussed an equivalent efficacy with intralesional corticosteroid injections as compared to systemic corticosteroids. This study cautioned regarding the rare risk of inadvertent intravascular/ophthalmic artery embolization

Table 10. Summary of studies on side effects of oral propranolol in treating capillary haemangiomas

Author	Number of patients	Dose of oral propranolol	Number of side effects reported	Side effects
Sans et al[37] 2009	13	2-3mg/kg/day	1	Wheezing
Li et al[42] 2010	4	2mg/kg/day	none	
Haider et al[44] 2010	17	2mg/kg/day	6	Gastrointestinal upset, intermittent fatigue, spitting, shaking episodes
Cheng et al[45] 2010	10	2mg/kg/day	none	
Claerhout et al[39] 2011	10	2mg/kg/day	1	Wheezing
Harikrishna et al[46] 2011	4	2mg/kg/day	none	
Missoi et al[47]2011	17	2mg/kg/day	1	Bradycardia
Snir et al[43] 2011	30	2mg/kg/day	11(treatment discontinued in 1, dose reduced in 3)	Respiratory tract infection, breathlessness, loss of appetite, diarrhoea, vomiting, sleep problems, restlessness, fever
Léauté-Labrèze et al[48] 2015	456 (318 facial haemangiomas)	a) 55 patients placebo b) 98 patients 1mg/kg/day for 3 months c) 102 patients 1 mk/kg/day for 6 months d) 100 patients: 3mg/kg/day for 3 months e) 101 patients 3 mg/kg/day for 6 months	26 patients had serious adverse events a) 3 b) 5 c) 3 d)9 e)6	Hypotension, bradycardia, bronchospasm, hypoglycaemia Others: diarrhoea, sleep disturbance, agitation, vomiting, cold extremities, constipation, decreased appetite
The present study	10	3mg/kg/day	3	Lethargy, poor feeding

with permanent visual loss during administration.[30] The most serious and feared complication is central retinal artery occlusion (CRAO).[29] Bang et al recommended that while administering intralesional corticosteroid, retinal vessels should be examined during and after injection to monitor for central retinal artery occlusion. It has been speculated that increased force from the injection or digital pressure after the procedure may cause retrograde flow of the drug particles into the central retinal artery.[18] Though this has been documented with steroid injection, it may be a potential risk with intralesional propranolol also. Awadein et al compared intralesional propranolol injection and intralesional triamcinolone in periocular capillary haemangiomas and they did not report any adverse effects during or after intralesional propranolol injection.[21]

In the present study, none of the ten patients in group 2 (intralesional propranolol) reported any side effects, local or systemic. All the injections were administered under general anaesthesia with cardio respiratory monitoring. As compared to the study by Zaher et al, pain was not a reported side effect both during the injection procedure and subsequently in the observation period.[19] None of the patients in the present study reported any side effects related to the general anaesthesia. However, it is pertinent to highlight the potential side effects and the need for general anaesthesia for the procedure, given the age group of these patients. Older children may be cooperative for the procedure under topical anaesthesia. Alternatively, the procedure may be undertaken under sedation with peri-operative analgesia. This may add to the logistics of the procedure. In addition, pre and post anaesthesia care is required with monitoring of systemic parameters including heart rate and respiratory rate. These are summarised in table 11.

To summarise, in contrast to two studies published by Zaher et al and Torres-Pradilla et al, in the present study we found a statistically comparable response at 6 months with intralesional propranolol as compared to oral propranolol.[19,22] Within the group receiving intralesional propranolol, we retrospectively compared the baseline characteristics of the patients having excellent or very good response with an area reduction >70% at 6 months (group 2a, n=5) with the remaining patients who showed a lesser response (group 2b, n=5). The lesions, which showed an excellent or very good response, had a smaller size at baseline. The overall percentage area reduction in this group (group 2a) was 85.28% (range 72.65% to 92.31%). As compared to this, the

Table 11: Summary of studies on side effects of intralesional propranolol in treating capillary haemangiomas

Author	Number of patients	Dose of oral propranolol	Number of side effects reported	Side effects
Awadein et al[21] 2011	12	1mg/ml Single injection 0.2ml/cm GLD, maximum of 1ml Dilated fundus exam done during injection, administered under general anaesthesia	None	
Zaher et al[19] 2013	15	1mg/ml 0.2ml/GLD weekly injections administered 60 min after topical a naesthesia with lidocaine	3	Severe pain during injection
Torres-Pradilla et al[22] 2013	6	1mg/ml, 0.2ml/cm of GLD Injection repeated if response seen at 1 month	6	Pain (all patients), erythema
The present study	10	1mg/ml propranolol hydrochloride 0.2ml/cm of longest linear dimension (maximum of 1 ml) 3 injections 4-6 weeks apart, administered under general anaesthesia		

overall percentage reduction in area in group 2b was 50.28% (range 31.48% to 69.1%). This difference in these two groups was statistically significant with a p value of 0.0018. Thus, small, localized lesions showed significantly better response to intralesional propranolol.

Studies to analyse local concentration of drug after intralesional administration and detailed histopathological analysis to assess effect of injection procedure on the lesion can help better delineate the mode of action of intralesional propranolol and highlight its differences as compared to oral propranolol. In addition, development of a depot formulation of propranolol for intralesional administration may help in improving its efficacy.

The response seen in the present study in both groups was attributed to the treatment intervention. It could have however occurred as a part of the natural course of the regression of the haemangioma. The median age in the present study was 8 months (range 3-12 months) in group 1 and 10 months (range 5-60 months). Thus majority of the lesions were in the proliferating phase. However, in the absence of a control observation-only group, we can't comment conclusively on this finding.

SUMMARY

This was a prospective randomized control trial with 20 patients, 10 received oral propranolol (group 1) and 10 received intralesional propranolol (group 2). The baseline characteristics were comparable in both groups (except gender). Serial follow up was maintained and the final evaluation was done at 6 months.

Both groups responded well to treatment in terms of percentage area reduction. The average percentage area reduction in group 1 (oral propranolol) was 83.48% ±11.67% at the end of six months (p value 0.0019). The average percentage area reduction in group 2 (intralesional propranolol) was 67.78% ± 21.71% (p value 0.0019). There was no significant difference between the comparative reduction in percentage area in group 1 and 2 (p value: 0.056)

There was a significant change in colour of the lesions in each group (p value group 1: 0.04 and group 2: 0.02). There was a statistically significant greater improvement in colour in group 1 as compared to group 2 (p value: 0.021). There was no significant difference in the comparative reduction in appearance (from elevated to flat; p value 0.085) and reduction in ptosis (severe to mild; p value: 0.23) between the two groups. There was a 60.53% reduction in dioptric amount of astigmatism in group 1 and a 53.54% reduction in dioptric amount of astigmatism in group 2. (p values: Group 1: 0.0045 and Group 2: 0.0001). Thus both groups showed a significant reduction in astigmatism with treatment and the reduction was comparable between the two treatment groups (p value 0.49). Within group 2, small, localized lesions showed significantly better response to intralesional propranolol as compared to larger lesions.

No patient reported any side effects in the intralesional group in the present study compared to 3 patients having lethargy/ poor feeding in the oral group (p value 0.171, statistically non-significant).

Thus, intralesional propranolol may be considered a viable alternative to oral propranolol for periocular capillary haemangiomas. It may be considered as a first line therapy in small surface localized capillary haemangiomas. It may also be considered an alternate treatment in patients already on oral propranolol showing significant systemic side effects. A randomised control trial with a larger sample size, an observation only control group and a longer follow up should be done to conclusively determine the beneficial role of intralesional propranolol.

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This Paper was judged as the **BEST PAPER** of **ORBIT & OCULOPLASTY II** Session.

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Orbital Implant Migration: Are We Thinking Correctly?

Dr. Tarjani Dave

ABSTRACT

KEYWORDS

Orbital implant, 3D Printing, Migration, Custom designed, Secondary implant, Computer assisted

PRECIS

This study highlights the role of treating implant migration by placing a patient specific second orbital implant to re-center the migrated implant using rapid prototyping and 3D printing in ophthalmic plastic surgery. All 6 patients with inferotemporal implant migration had recentration of the implant over a mean follow up period of 24 months.

AIM

To determine whether a 3D printed patient specific implant (PSI)

placed sub-periosteally centers spherical orbital implant post enucleation.

METHODS

This is a single-center prospective consecutive interventional case series of 6 patients undergoing 3D printed, patient specific implant, for the correction of a non-porous spherical implant migration. Implant migration was assessed clinically and on patient photographs. Migration was sub-classified either as decentration that did not affect the prosthetic retention, or as displacement that affected the prosthetic retention in the eye socket. The primary outcome measure was centration of the implant clinically and radiologically with ability to retain the prosthesis. The secondary outcome measures were the mean PSI volume, volume of the custom ocular prosthesis (COP) and implant related complications like exposure and extrusion and migration of either implants.

RESULTS

At a mean follow up of 24 months, all six orbital spherical implants remained centered. There were no cases of PSI displacement. The mean PSI implant volume was 3.05 + 0.65 milliliters (ml). There were no cases of implant extrusion, exposure or repeat migration of either implants. The mean COP volume was 2.39 + 0.68 ml. Additional procedures to optimize the aesthetic outcome of the COP were required in 5 patients for this cohort. Simultaneous fornix formation suture was performed in 2 patients, fornix formation with mucus membrane graft in 1 patient, Levator resection in 1 patient and Sulcus filler injection in 1 patient.

CONCLUSIONS

This paper describes a novel approach to treat migrated orbital implants post socket surgery. A 3D printing assisted PSI allows recenteration of the migrated implant centrally over a long follow up period of 2 years.

INTRODUTION

Orbital implant migration following evisceration or enucleation surgery has been observed with porous as well as non-porous implants.[1] When the migrated orbital implant affects prosthesis placement and centration surgical correction of migration is required. Treatment

options include implant exchange and dermis fat graft.[2,3] Secondary orbital implants have a 25% rate of resurgery of which 13% is attributable to implant migration.[3] Dermis fat graft though an option involves a second site scar that may be unacceptable to many patients. In previously operated sockets the rate of graft necrosis is higher.[4]

3D printing technology along with computer aided design and prototyping is currently being used in the treatment of complex orbital fractures.[5] Using these techniques, an individual prototype skull model that resembles the patients orbit can be obtained before surgery.

In the present study we describe a novel, cost effective, minimally invasive technique of designing a patient specific orbital implant using 3D printing of the patients orbit.

METHODS

Study approval, Design and Subjects

This is a single-centre prospective consecutive case series including patients with socket surgery presenting with inability to retain the prosthesis due to implant migration. Institutional Review Board (IRB)/Ethics Committee approval was obtained. All patients presenting to the ophthalmic plastic surgery service or the ocular prosthesis laboratory between January 2014 to December 2016, with the complain of frequent loss of prosthesis form the eye socket were assessed for the presence of infero-temporal implant migration. Migration was classified as decentration and displacement based on our previous work. Six patients had infero-temporal implant displacement with inability to retain the prosthesis and were included in the study. All 6 patients had implant palpable anterior to the inferior orbital rim with consequent shallowing of the inferior fornix. Patients with contracted socket but central implant were excluded. All patients received a PSI custom designed with the aid of 3D printing and rapid prototyping. The cases operated by a one faculty in the service (TVD). All patients had a custom ocular prosthesis (COP) placement at the two months post-operative visit. Additional procedures required either along with the PSI placement or in the follow up period of 2 years were documented.

Outcome measures

The primary outcome measure was the recentration of the spherical implant migration and the ability to retain the prosthesis. The secondary

outcome measures were the mean PSI volume, diameter of the migrated implant, volume of the COP and other post-operative complications.

Data Collection

The data collected included the demographic details, the indication for surgery and the past ocular procedures, PSI fabrication time, the surgical technique and the surgical steps as detailed in the medical records. Socket examination findings pre-operatively and at the two-month, six-month, I year and 2 year postoperative visit included the (a) examination of the socket with the prosthesis, (b) examination of the socket without the prosthesis and (c) the examination of the prosthesis. The pre and post-operative CT scan was assessed for centration of the migrated implant, the position of the implant in the orbit along the x,y and z axis.The post-operative complications like recurrent implant migration, exposure and extrusion if present were looked into.

SURGICAL TECHNIQUES

3D printing details

DICOM images from the computed tomography scan were rendered as 3D models and the region of interest around the orbit was segmented and exported as a binary STL. This was sliced into several 2D layers using proprietary 3D printing software. To build an accurate 3D model, support structures were generated to provide structural integrity to the model being 3D printed. Distinct tool paths were generated for the model and the support structures in CMB format, which was then 3D printed in the Stratasys Fortus 250 mc, an additive manufacturing system that employs Fused Deposition Modeling (FDM). 3D printing was done at 178 micron layer thickness and with high-density infill to get a rigid model. The model was 3D printed with Stratasys ABS P430 material and supporting structure was made with Stratasys ABS SR30. Once the 3D printed model was ready, the support structures were dissolved in an ultrasonic agitation tank resulting in the final orbit model (figure 2A).

Custom implant fabrication

Using this skull model as a mould, a PMMA implant was fabricated to sit in the basin of the inferior orbital fissure (figure 2B) of this patient to push the migrated implant centrally. The implant was sterilized prior to surgery.

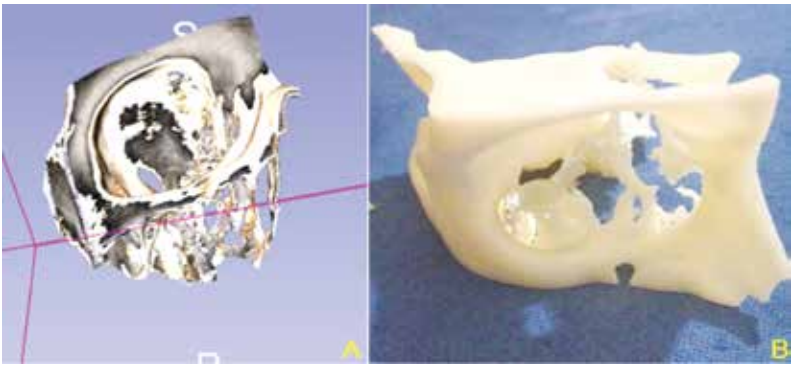

Fig.2: Skull models in soft copy and 3D. 2A: Skull model built in 3D using DICOM images of the patients CT orbit. 2B: skull model printed in plastic and used as a mould to fabricate an orbital implant from PMMA.

Surgery details

Through an inferior transconjunctival approach the periosteum was incised just within the orbital margin and reflected to expose the basin of the inferior orbital fissure. The customized orbital PMMA implant was placed subperiosteal, conforming to the pre-designed shape of the floor of the orbit. The recentration of the pre-existing spherical implant was checked for on table by palpating through the palpebral fissure and post-operatively with CT orbit at 6 weeks. Conjunctiva was closed and inferior fornix forming sutures were taken when necessary. Conformer was placed and suture tarsorrhaphy was performed.

Statistical Analysis

The data were arranged on an excel spreadsheet. Relevant statistical analysis was done using MedCalc version 12.2.1.0. Continuous parametric data were reported as mean (+ standard deviation) and non parametric data were reported as median with range. Variables between comparative groups were compared using paired t test for parametric distribution and Mann-Whitney U test for non-parametric distribution. A P value of < 0.05 was assigned as statistically significant.

RESULTS

Case 1

This is the pilot case treated by this technique. A 16 year old male patient presented to us for a tilted and unstable custom ocular prosthesis. On examination, he had a decentred prosthesis with its inferior edge resting on the lower eyelid margin (figure 1A,C). This was resulting

in frequent fall of prosthesis from the socket. There was shelving of the inferior fornix with inferotemporal migration of the orbital implant (figure 1B). The implant was palpable anterior to the inferior orbital rim. There was no apparent conjunctival surface loss. Volume loss was evident in terms of the superior sulcus deformity. Computed Tomography scan of the orbit showed an 18 mm orbital implant migrated inferotemporally into the extraconal space (figure 1D). He had undergone three socket surgeries in the past starting with an evisceration with implant for a painful blind eye followed by implant exchange twice for inferotemporal implant migration. Owing to the recurrent inferotemporal implant migration we anticipated fibrosis in the orbit and hence did not consider an implant exchange. The patient denied dermis fat graft due to donor site morbidity. Hence we decided to place a customized implant in the inferotemporal orbit that would push the migrated implant centrally. The surgical steps were as discussed in methods. Six weeks postoperatively, CT scan of the orbit showed the customized orbital implant in place and with intraconal migration of the spherical implant (figure 3C). A customized ocular prosthesis remained stable and central thereafter till his last follow-up of 2.5 years (figure 3A,B,D).

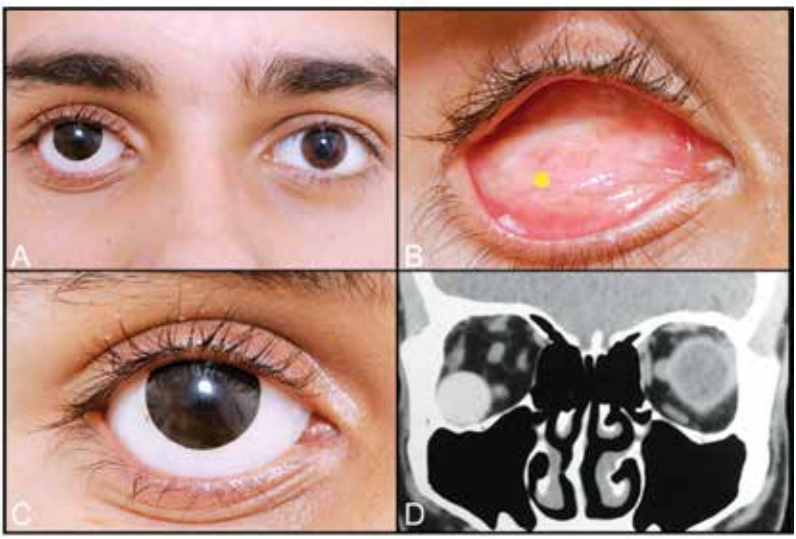

Fig.1: Figure 1:Pre-operative examination details. 1A: Right decentered prosthesis with superior sulcus deformity, 1B:Inferotemporal migration of implant highlighted with shelving of the lower fornix, 1C: Inferior edge of the prosthesis resting on the lower eyelid margin with increased inferior scleral show, 1D: CT orbit in the coronal plane showing inferotemoral spherical orbital implant migration

The average volume and weight of all the other patients operated for PSI's and the demographics of the other cases are as described in table 1.

Sl No	Eye	Age/ gender	Prior socket surgery	Other ocular findings	Prior attempts at implant centration	Adjunctive procedures	Pre existent implant diameter	PSI implant volume cm^3	Final COP weight (gms)
1	OD	17/M	1. Enucle-ation + Implant 2. Implant exchange 3. Implant exchange	1. Shallow inferior fornix	2	FFS	18	2.70	2.05
2	OD	47/M	1. Scleral tear repair 2. Enu-cleation with implant	1. LL laxity 2. shallow inf fornix 3. SSD grade IV	None	Ptosis correction	18	2.50	1.75
3	OD	25/M	1. Enu-cleation + Implant 2. FFS + MMG 3. FFS 4. FFS +	1. LL laxity 2. Shallow Inf fornix 3. SSD	None	FFS + MMG	18	2.00	2.49
4	OD	21/M	1. Enu-cleation + Implant	1. Shallow inferior fornix 2. Grade II SSD	None	FFS	16	3.5	1.99
5	OS	45/F	1. Enu-cleation 2. Secon-dary Implant	1. Shallow inferior fornix 2. Grade IV SSD	None	Filler injection 1cc Supe-rior sulcus	18	3.00	3.80
6	OD	3/M	1. Enu-cleation + Implant	1. Shallow inferior fornix	None	None	18	2.30	1.90

None of the 6 patients developed complications of the spherical or patient specific implant over a mean 24 month follow up. Two patients underwent a simultaneous inferior fornix formation suture for shallow inferior fornix. One patient underwent a subsequent fornix formation suture and mucus membrane graft for grade 1 contracted socket with shallow inferior fornix. One patient required a levator reinsertion for anophthalmic ptosis and one patient had persistent severe superior sulcus deformity for which a hyaluronic gel filter was injected in the superior fornix. The mean pre- operative and post-operative COP weight were 2.86+1.06 and 2.4+0.82 (p=0.4). The mean PSI implant

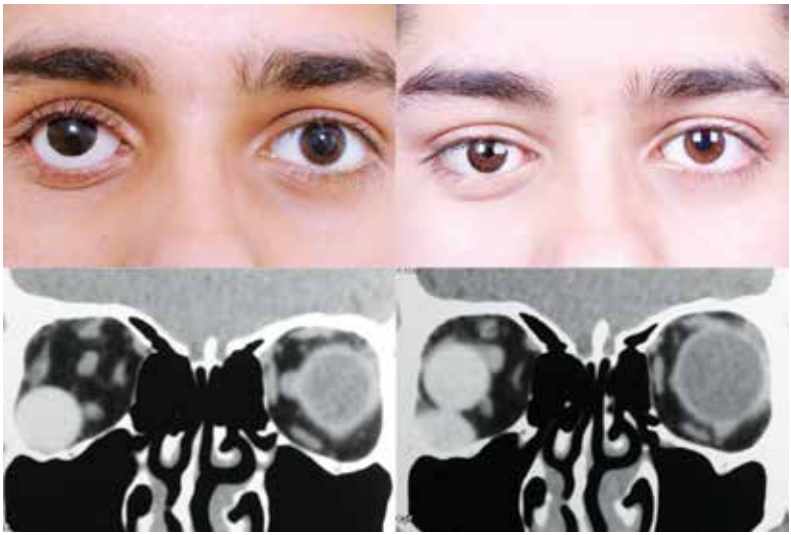

Fig.3: Comparison of pre and post-operative result.3A: Pre-operative standard view photograph of the patient with superior sulcus deformity and decentred ocular prosthesis, 3B: Post-operative standard view photograph of the patient with correction of the superior sulcus deformity and a better fitting ocular prosthesis. 3C: Pre-operative CT orbit of the patient showing an inferotemoralmigrated spherical orbital implant. 3D: Post-operative CT showing a patient specific implantpushing the spherical implant towards the central intraconal space.

weight was 2.6 cm^3. The mean pre and postoperative enophthalmos was 1.8+1.32 mm and 0.6+1.21 mm. The mean preoperative superior sulcus deformity was grade 2 preoperatively and grade 0 postoperatively. There was no reduction in the ocular motility post surgery with the patient specific implant.

DISCUSSION

This study shows that placing a second sub-periosteal implant in the quadrant of migration can center inferotemporal migration of spherical orbital implant following enucleation. This second implant can be custom configured such that it allows exact centration of the spherical implant. The use of 3D printing and rapid prototyping technology allows for the required shape and size configuration of the patient specific implant. This reduced the chances of further implant complications such as migration, exposure and extrusion. To the best of our knowledge this is a novel application of 3D printing technology in ophthalmic plastic surgery with promising results.

Non-porous implants suffer a higher rate of implant migration compared to their porous counterparts especially in the setting of

enucleation.[6,7] However in the absence of pegging, a porous implant does not provide additional motility compared to a non-porous implant.[8-10] Hence several surveys have shown that a significant proportion of surgeons prefer to place a non-porous implant following socket surgery.[9,10] While the non-porous implant offers an excellent and comparable outcome to its porous counterpart, one of the important disadvantages is implant migration since it is devoid of fibrovascular tissue ingrowth into the implant.[11]

Implant migration has been poorly studied in literature. In our opinion the cause of implant migration seems to be orbital fibrosis or disturbances in the Koornneef's septa that are present between the extraocular muscles and divide the orbit into its extra and intraconal spaces.[12-19] Once these septa are disturbed or damaged during socket surgery the chances that an implant may migrate increase. This is specifically true in case of enucleation where there is more disturbance of the orbital anatomy versus evisceration. All the 6 patients in our series suffered implant migration following enucleation.

With this background knowledge, that it's the orbital fibrosis and disturbance in the orbital anatomy that increases the risk of non-porous implant migration, it is most certain that an implant exchange with non-porous implant will not help in recentering a migrated spherical orbital implant. The use of a porous implant for implant exchange may be an alternative, however a theoretical risk of the porous implant remaining migrated exists since we have established that it's the orbital fibrosis that is responsible for migration of the implant. Also the cost of a porous implant is approximately $ 200 vs that of a non-porous implant which is $ 20-25.[20] This leaves us with the option of dermis fat graft for volume augmentation in patients with a migrated spherical non-porous implant. However the requirement for a second site incision and the higher rate of graft necrosis in repeat socket surgeries makes this procedure an unattractive choice.[21,22]

3D printing and rapid prototyping has been used in ophthalmic plastic surgery for the correction of complies orbito-zygomatic fractures and in creation of patient specific implants for volume augmentation in the orbit.[23,24] 3D printing and computer-assisted techniques allow for the creation of the patients orbit in vitro and this serves as a mould for fabrication of the patient specific implant. With the use of freely available softwares such as MIMICS, it is possible to compute the PSI and directly print the implant using the readily available, inexpensive, range of materials in plastic that can be 3D printed. This implant can

then be converted to a PMMA model using the same techniques as those of fabricating a custom ocular prosthesis.

The limitations of this study include, lack of histo-pathological documentation of fibrosis in the orbit as a cause for implant migration, a smaller patient cohort and a relatively shorter duration of follow up. The cost effectiveness of the treatment has been calculated by taking into account only the cost of 3D printing and not the additional cost of fabrication of the PSI implant. However since we used PMMA for the fabrication of the PSI, it still remains an inexpensive alternative. The procedure does involve placement of a second implant in the orbit and this increases the risk of implant related complications. The mean follow-up duration of 24 months may be a limitation, however no complication related to both the implants were seen over this follow up duration. We do recommend a longer follow up of these cases.

CONCLUSION

Patient specific orbital implant fabrication using 3D printing and additive manufacturing offers a novel and cost-effective way to centre orbital implants in patients with recurrent implant migration. This is especially true for patients who have associated volume loss. Pre-operative 3D Printing enables us to determine the exact shape and size of the patient specific implant.

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COMPETING INTERESTS

none

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This Paper was judged as the **BEST PAPER** of **PAEDIATRIC OPHTHALMOLOGY 1 -** Session.

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Altered Tear Dopamine – Biomarker For Pediatric Myopia

Dr. Jyoti Matalia, Dr. Prathibha Panmand, Dr. Pooja Ghalla, Dr. Rohit Shetty

INTRODUCTION

Literature review has shown that local dopamine levels play a role in propensity to development of deprivation myopia and lens induced myopia but most of the studies done about dopamine and refractive errors were mainly in animal models. However, there has been no study comparing the levels of tear dopamine in normal and myopic eyes. We are investigating the role of dopamine in development of refractive errors by measuring the levels of dopamine in tears. This

study was done to see if this non-invasive method of tear collection and tear dopamine level evaluation could provide us any actual correlation in human eyes with reference to myopic refractive errors.

PURPOSE

To study the dopamine levels in the tear fluid (non-invasive) in myopic children and correlation of thedopamine levels between emmetropes and different grades of myopia.

MATERIAL AND METHODS

The study was conducted at a tertiary care centre after obtaining ethics committee approval.

INCLUSION CRITERIA

Patients less than 18 years reporting at the pediatric OPD having signs and symptoms pertaining to refractive error. Children with myopia were included in the study. Myopia was classified into low (-1.5 DS to -2.5 DS), moderate (-4.0 DS to -5.0 DS) and high myopia (-6.5 DS to -8.0 DS). Healthy volunteers with no ocular conditions were recruited for the relevant control groups.

EXCLUSION CRITERIA

The following subjects/patients were excluded from the study.

1. Those with recent (last three months) history of eye allergy or infection
2. Those with any underlying systemic autoimmune or other inflammatory conditions
3. Those wearing contact lenses
4. Those who have recent history of surgical or medical treatment for an ocular condition
5. Those with known general malnutrition
6. Those on any systemic medications.

On the basis of the above, 30 children with different grades of myopia and 10 emmetropes were included in this study. All children underwent detailed ophthalmic evaluation including cycloplegic refraction, anterior and dilated posterior segment evaluation. Axial length was measured using A-scan using IOL Master.

Tears were collected from all over Schirmers strips, stored at -80 deg C and analysed by flow cytometry. Total dopamine level in the tears was measured by competitive inhibition enzyme linked immunoassay.

STATISTICAL ANALYSIS

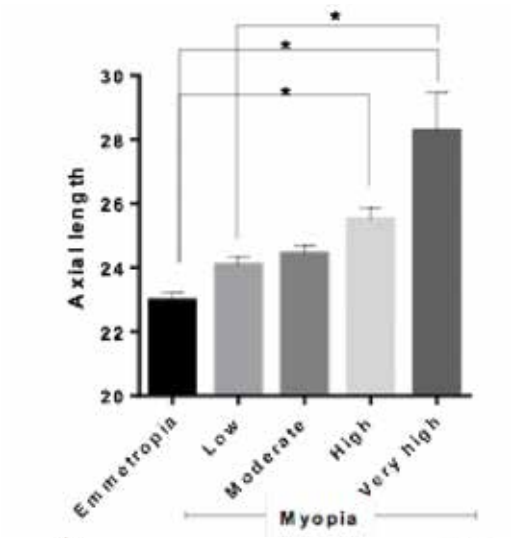
All statistical analyses were performed with Graph Pad Prism 6.0 (Graph Pad Software, Inc., La Jolla, CA, USA). Shapiro-Wilk normality test was used to check distribution of the data set. Spearman correlations analysis, Kruskal-Wallis and Mann-Whitney test were used to analyze data sets that were not normally distributed. The mean value of the individual groups was reported as mean ± SEM. $P < 0.05$ was considered to be statistically significant.

RESULTS

Ten emmetropes, 10 low, 7 moderate and 13 high myopes were included.

- Average age of children in emmetrope group was 11.8±1.1 years and myopia group was 11.4±0.6 years.
- There were 4 females and 6 males in the emmetrope group while there were 14 females and 16 males in the myopia group. No difference was observed in the tear dopamine levels between the male and female subjects.
- Mean axial length was 22.9 ±0. 2 mm in emmetropes and 25.3 ±0.3 mm in myopes.

Grade/severity dependent increase ($p < 0.05$; Mann Whitney Test) in the axial length across grades of myopia was observed but was not statistically significant.



Negative correlation ($r = -0.8215$; $p < 0.0001$) was observed between spherical equivalent and axial length measurements in the study subjects. These observations confirm that the subjects recruited for the study is appropriate.

- No correlation was observed between tear dopamine levels and axial length.
- Average dopamine tear levels in emmetropes were 1158±650 pg/ml while in myopes it was 165± 74pg/ml. The tear dopamine levels were observed to significantly ($p < 0.05$) lower in the myopic subjects compared to emmetropes
- The dopamine tear level amongst different grades of myopes:
    - Low myopia: 58±20pg/ml,
    - Moderate: 69±15pg/ml
    - High: 143±82pg/ml.

No significant difference in the tear dopamine levels between the grades/severity of myopia was observed.

CONCLUSION

This study suggests a possible role of tear dopamine as a biomarker for predicting progressive myopia in children.

1. Significantly low level of dopamine was observed in myopia compared to emmetropia
2. It was observed that there is very less difference in levels of dopamine within the subgroups except in the pathologic group which is relatively high but the difference in tear dopamine levels within the myopic subgroups was not significantly different and to detect a trend a study with larger sample size in subgroups may be needed.
3. There is a negative correlation between axial length and spherical aberration.
4. Finally there is no correlation observed between dopamine and axial length and also between dopamine and spherical aberration.

This Paper was conferred with the AIOS-HANUMANTHA REDDY AWARD for the BEST PAPER of PAEDIATRIC OPHTHALMOLOGY Session. This paper was also judged as the BEST PAPER of PAEDIATRIC OPHTHALMOLOGY II Session.

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Intra-Arterial Chemotherapy For Retinoblastoma: Three-Year Results

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INTRODUCTION

Treatment of retinoblastoma (RB) is rapidly evolving and ever changing. Management options include enucleation, radiotherapy, chemotherapy and focal therapy. The four routes for delivering chemotherapy are intra-venous (IVC), intra-arterial (IAC), peri-ocular, and intra-vitreal (IVitC). Focal therapy includes laser photocoagulation, transpupillary thermotherapy (TTT), and cryotherapy. External beam radiotherapy (EBRT) has now become obsolete due to the risk of secondary non-ocular tumors and was replaced by intravenous chemotherapy (IVC) in the 1990s.[1,2,3] Enucleation rates have steadily declined as high rates of globe salvage can now be achieved using various forms of chemotherapy. Still, enucleation remains an important option in advanced RB, especially in developing countries of Asia and Africa.[4,5] Even in ICRB (International Classification of Retinoblastoma) Group E eyes, intra-arterial chemotherapy (IAC) and IVC are offered as options to save the eye. In unilateral, non-germline Group B to group E RB, IAC is now considered as a primary option in select cases. Secondary IAC is used for recurrent tumors, subretinal seeds, and vitreous seeds. IVC is used as first line treatment modality for bilateral, familial RB (germline RB) for intraocular tumor control and prevention of metastasis. Intravitreal chemotherapy is used for recurrent vitreous seeding.[6] IAC offers the advantage to reduce systemic chemotherapy related complications like neutropenia, anemia and secondary neoplasms.[7] It decreases the duration of hospital stay and allows delivery of high dose chemotherapy directly to the tumor bed.[8] Reduced systemic absorption also allows the use of melphalan, which has been found to be the most effective chemotherapeutic agent in RB.[9] Concerns with the use of IAC include its efficacy in advanced

Group E tumors and recurrence rates in tumors with vitreous seeding; high economic burden especially in developing countries; rates of useful vision salvage despite high globe salvage and complications. Complications in IAC can occur due to the technique of the injection itself and from the use of a high dose of chemotherapeutic agents which can lead to ocular and systemic toxicity.

We have previously reported the one-year and two-year efficacy and complications of IAC for RB. In this study, we seek to share our three-year experience of IAC for RB at a tertiary eye-care hospital in India.

MATERIALS AND METHODS

This is a retrospective, interventional case series which includes 15 eyes of 15 patients with RB treated by IAC at the Oncology Service between November 2013 and July 2017. Institutional Review Board approval was sought. Written informed consent was taken from the parents of all patients after a detailed explanation of the risks and potential benefits of treatment. The tenets of the Declaration of Helsinki were adhered to. The study included subjects with unilateral or bilateral Group B to E retinoblastoma. The patients may or may not have received prior systemic chemotherapy. Data collection included demographic details, details of presenting features, clinical findings, management, complications, and outcomes. Relevant family history was noted. History of past ocular and systemic treatment was taken. A comprehensive ophthalmic examination was performed under anesthesia. Details of the ophthalmic examination, ancillary and systemic investigations have been described by us in a previous study. Documentation of retinal findings was done with fundus drawing and fundus photography with RetCam camera (Massey Industries, Dublin, CA, USA). The international classification of retinoblastoma (ICRB) was used to group the tumors. The IAC catheterization procedure, chemotherapy dosing and follow-up schedule have been described by us previously. Primary outcome measures included tumor regression, VS and SRS control, globe salvage at final follow up. Secondary outcome measures were best corrected visual acuity (BCVA) at final follow up and treatment complications.

RESULTS

The mean age of the patients at treatment was 30.4 months (median: 24, range: 11-94 months). All 15 patients had sporadic RB. The various modes of presentation were leukocoria (n = 7), strabismus (n = 1),

both (n = 4), diminished vision (n=1) and redness of the eye (n = 2). Mean duration of symptoms at presentation was 9.1 weeks (median: 3, range: 0–48 weeks). Eyes with RB were grouped as per the international classification of RB (ICRB) as Group A (n=0), Group B (n = 1), C (n = 3), D (n = 9) and E (n = 2). Baseline tumor characteristics at first EUA were noted. The mean tumor base at baseline was 17.1 mm (median: 18, range: 6–24 mm) and the mean tumor thickness was 7.4 mm (median: 8.2, range: 2.6-11.5 mm). Vitreous seeds (VS) were present at base-line in 12 eyes with involvement of 1 quadrant (n = 1), 2 quadrants (n=5), 3 quadrants (n = 1) or all 4 quadrants (n = 5). Subretinal seeds (SRS) were present at baseline in 6 eyes involving 2 quadrants (n = 2), 3 quadrants (n = 2) or all 4 quadrants (n = 2). Optic nerve was visible in seven eyes, partially visible in one eye and obscured due to tumor overhang in seven eyes. Exudative retinal detachment secondary to the tumor was present in six eyes (15-100%). Six eyes had a single tumor at presentation. Of the remaining nine eyes that had multiple tumors, the number of tumors per eye ranged from 1 (n = 6), 2 (n = 5), 3 (n = 2), 4 (n=1) or 5 (n = 1). Eight eyes (53.3%) had predominantly exophytic tumors while seven eyes (46.7%) had predominantly endophytic tumors. Mean proximity of tumor to optic disc was 1.5 mm (median: 0, range: 0–16 mm) and to the foveola was 2.1 mm (median: 0, range: 0–20 mm). IAC was employed as either primary (n = 6) or secondary (n = 9) modality of systemic therapy. Nine of 15 patients had bilateral RB. Of these, fellow eye of 6 patients underwent enucleation for Group E tumor. Prior treatment with intravenous chemotherapy using vincristine, etoposide and carboplatin (VEC) is as follows: 1 cycle (n=1), 3 cycles (n=2), 4 cycles (n=1), 6 cycles (n=2), 7 cycles (n=1), 9 cycles (n=1) or 11 cycles (n=1). Local treatments included cryotherapy (n = 10), transpupillary thermotherapy (n = 5), external beam radiotherapy (n=1) and combination intravitreal chemotherapy with melphalan and topotecan (n = 1; Case 9)

Tumor characteristics before IAC, treatment details, ocular complications and outcomes are mentioned in Table 2. Each eye received mean 3.53 IAC sessions (median: 3; range: 1–5 sessions). Additional systemic chemotherapy included VEC for 2 cycles (n = 2), 3 cycles (n = 1), 5 cycles (n = 1), 6 cycles (n=4) or 8 cycles (n=1). Local therapy included cryotherapy (n = 14), transpupillary thermotherapy (n = 11) and combination intravitreal chemotherapy with melphalan and topotecan (n = 5).

At the last follow-up following IAC, complete regression of the main tumor was seen in 8 eyes (53.3%), partial regression in 4 eyes (26.7%), persistence of tumor in one eye (6.7%), and recurrence in two eyes (13.3%). Twelve eyes had active VS at baseline, of which six eyes (50%) showed complete regression, one eye (16.7%) showed partial regression, two eyes (8.3%) showed persistence, while 3 eyes (25%) showed recurrence. Six eyes had subretinal seeds at baseline. Of these, five (83.3%) had completely regressed after the last IAC session, while one eye (16.7%) showed recurrence. Globe salvage was achieved in 12 of 15 (80%) eyes and three eyes underwent enucleation during the course of treatment (Case I,II and XII); case I due to dense vitreous haemorrhage after fourth IAC session; case II and XII due to development of retinal detachment and recurrence of tumor. Kaplan Meier survival curve showed 91% globe survival rate at 18 months after the first IAC session, 82% at the end of 18 months, 70% at the end of 24 months and remained stable at 70% at the end of 36 months. Histopathologic examination revealed poorly differentiated RB with choroidal invasion more than 3 mm in all three cases. There was involvement of post-laminar optic nerve and ciliary body infiltration in Case 2 and anterior sclera involvement in case XII. All cases underwent adjuvant chemotherapy using VEC.

Complications included transient ophthalmic artery narrowing (n=2), branch retinal vein occlusion (n = 1), vitreous hemorrhage (n=3), sclerosed vessels (n = 1), toxic optic neuropathy (n=1), optic atrophy (n=1), iris atrophy with posterior synechiae (n=1), posterior subcapsular cataract (n = 2), forehead skin pigmentation (n = 1) and allergic skin reaction (n=1). There was no stroke, hemiplegia, metastasis or death in any patient. Transient hematological changes included relative pancytopenia (n = 4), relative leukopenia (n = 5), relative thrombocytopenia (n = 4), eosinophilia (n=2) and relative lymphocytopenia(n=1). None of the patients had metastasis or death.

In summary, we describe the outcomes of IAC for RB at 3 years from a single, tertiary eye-care centre in India. IAC is effective in achieving higher rates of globe salvage in eyes with intra-ocular retinoblastoma.

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Comparison Of ICL Sizing Using WTW (White To White) And ACD (Anterior Chamber Depth) Measurements From Different Devices

Dr. Lalgudi Ganesh Vaitheeswaran, Dr. Hema Malini, Dr. Mathew Kurian, Dr. Rohit Shetty

ABSTRACT

PURPOSE

To compare the ICL sizing obtained using WTW and ACD from Orbscan II, Lenstar, Nidek OPD scan III and Galilei and assess its impact on the predicted vault.

METHODS

The WTW and anterior chamber depth from Orbscan (Bausch & Lomb) were used to calculate the ICL size. The predicted vault was calculated from the UBM (Quantel Medical) machine and achieved vault measured by the AS OCT (Casia). In patients with normal predicted and achieved vaults, the ICL size was also calculated using the WTW from the Lenstar, Nidek OPD scan III and Galilei with the standard ACD from Orbscan and also their respective ACDs, except for Nidek OPD III scan. Predicted vaults in each situation was compared with the achieved vault.

RESULTS

54 eyes (31 OD, 23 OS) of 54 patients underwent uneventful ICL implantation. The mean WTW from Orbscan was 11.56 +/- 0.35 mm, Lenstar was 12.16+/- 0.47 mm, Galilei was 12.02 +/- 0.35 mm and Nidek OPD scan III was 12.32+/- 0.44 mm. Mean ACD from Orbscan was 3.14+/- 0.18 mm, Lenstar was 3.66 +/- 0.19 mm, Galilei was 3.75 +/- 0.18 mm, UBM was 3.27+/- 0.19 mm. Using the ACD from Orbscan and WTW from the different devices, ICLs were oversized by 2 sizes compared to Orbscan in 5%, 11%

and 18% of patients by Galilei, Lenstar and OPDIII scans respectively and the same was in 10% and 20% of patients by Galilei and Lenstar when their ACDs were also considered.

The mean preoperative predicted vault by Orbscan was 0.56+/-0.11 mm, by Lenstar 0.70 +/-0.13 mm, by Nidek 0.71+/-0.12 mm, by Galilei 0.69+/-0.12 mm and the mean post-operative attained vault was 0.53 +/- 0.14 mm.

CONCLUSIONS

ICL sizes by Lenstar, Nidek OPD scan III and Galilei were oversized significantly compared to the sizes calculated by the Orbscan and with higher predicted vaulting. In considerable patients, they were further oversized when the ACD from Lenstar and Galilei were used for calculation. These patients stand a significant risk of high vault and complications. A correction factor is needed to accurately calculate the appropriate ICL diameter.

INTRODUCTION

The Implantable Collamer Lens (V4C) has been proven to be effective and approved by the FDA for the correction of moderate to high myopia.[1] There are still reports on complications and requirement of exchange of ICLs owing to high or low vault and its associated problems as pupillary block, pigment dispersion or cataract formation.[2] Majority of these problems stem out of the inaccuracy in the sizing of the lens which is surrounded by the controversy of WTW or STS (sulcus to sulcus) as a guide to the sizing.

With several studies[3-8] comparing WTW or STS based methods for the ideal sizing and outcomes ruling in favour of neither of them as the single best method, meta-analysis has shown that comparison between WTW or STS based methods result in no clinically or statistically significant differences in the overall attained vault.[9]

While STS can be measured by UBM machine only, WTW and ACD are being measured by numerous machines available in market. The correlation between WTW and STS has been found to be weak by studies.[4,10] With STS still not approved by the FDA and widespread non-availability of UBM among refractive surgeons, the current search is towards instruments that can give the ideal WTW and ACD for estimating the ICL sizing with accuracy.[11]

Among the instruments measuring WTW and ACD, studies have shown that the inter instrument variability is significant and they

cannot be used interchangeably,[12-14] but the amount of difference they generate in ICL sizing and its effect on the vault has not been studied to date. Some studies have shown the use of Orbscan II for WTW measurement to be safe and predictable for ICL size calculation and that other machines measure a higher WTW compared to Orbscan. But no method has been devised till date to calculate the WTW or ACD of a certain ideal device if the same parameters are known of another device. This could go a long way in helping refractive surgeons in low resource settings to be able to deliver safer outcomes in a larger number of patients.[11]

METHODOLOGY

Patients of high myopia with or without astigmatism willing for ICL/TICL implantation in the last 12 months were studied. All these patients underwent standard ICL sizing calculation using the WTW and ACD from Orbscan and keratometry, Pachymetry from Pentacam. Cycloplegic refraction and subjective acceptance was used to calculate the amount of refractive error to be corrected. UBM (Quantel Medical) was also done routinely to estimate the mean STS and predict the post-operative vault based on the ICL simulator software for the ICL size obtained (using STAAR ICL calculator). Post operatively, the attained vault was measured using the swept source based (Casia) ASOCT.

These patients, in addition to the routine work up, were subjected pre-operatively to WTW and ACD measurements using the Lenstar 900, Galilei G4 and Nidek OPDIII scan systems. All these devices automatically calculate these variables and hence there is no subjective difference between two different operators.

Post operatively, for all those patients who had a normal predicted and attained vaults (range of 250-750 micron), the ICL size was calculated with the WTW obtained from each of the other devices (Lenstar 900, Galilei G4 and Nidek OPDIII scan) using the online standard calculator. In the first step, the ACD from Orbscan was used with only variable being WTW and in the next step, ACD was also taken from the individual devices (except Nidek OPDIII scan) along with the WTW from the respective devices for ICL size calculation. The predicted vaults were also measured for the ICL sizes obtained using the ICL simulation method in the UBM done pre-operatively.

All the data including the refractive error corrected, age of patients, WTW and ACD from each of the devices studied, STS, ICL sizes

obtained using each of the above-mentioned methods were entered and analysed using MedCalc. Software.

RESULTS

54 eyes (31 OD, 23 OS) of 54 patients were included in the study. The Average age of patients studied was 29.35+/- 5.21 years (Range: 23- 42 years). The mean spherical equivalent corrected was 13.18 +/- 4.3 DS with 49 requiring Toric ICLs and remaining non toric ICLs. The mean WTW from Orbscan was 11.54+/-0.34 mm and the mean STS measured was 11.54+/- 0.49 mm. The mean ACD used from Orbscan was 3.15+/-0.19 mm. The WTW measured from the four devices showed significant difference with highest being that of Nidek OPDIII scan followed by Lenstar, Galilei and Orbscan, in that order (Table 1).

Table 1: Comparison of WTW between the devices studied (Mean, SEM and 95% confidence intervals are mentioned)

Factor	Mean	Std. Error	95% CI
WTW Galilei	12.0073	0.04672	11.9136 to 12.1009
WTW Lenstar	12.1253	0.05833	12.0083 to 12.2422
WTW OPD scan III	12.2944	0.05925	12.1756 to 12.4132
WTW Orbscan	11.5389	0.04557	11.4475 to 11.6303

The impact of the above differences in WTW on ICL sizing with respect to sizing based on Orbscan WTW were studied. The sizes obtained by all the three devices were oversized in most of the eyes, with only around 20% of eyes having the same size as obtained by Orbscan WTW and ACD. The maximum number of eyes significantly over sized (by 2 sizes) was with Nidek OPD III scan followed by Lenstar and Galilei. ICLs were oversized by 2 sizes compared to Orbscan in 5%, 11% and 18% of patients by Galilei, Lenstar and OPDIII scans respectively (Figure 1).

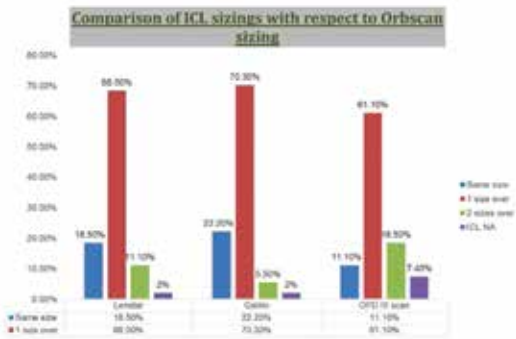

Fig.1: Shows the comparison of ICL sizes obtained using other machines WTW alone with that of Orbscan.

The means of predicted vault (based on UBM) by each of the devices were compared with the attained vault (measured by Casia ASOCT) and the distribution of the predicted vaults were also studied. The attained vault differed significantly ($p<0.05$) with the predicted vaults of all the devices except that of Orbscan ($p=0.09$). (Table 2a, 2b)

Table 2a, 2b: Comparison of means of attained vault with the means of predicted vault based on Orbscan WTW and with other devices WTW:

Mean Attained Vault		**0.5243+/-0.14 mm**
Mean Predicted Vault by Orbscan		0.5665+/- 0.11 mm
Mean difference		0.042 mm
P value		0.0919
Attained vs Predicted	**Mean predicted vault**	**P Value**
Galilei	0.6938 mm	<0.001
Lenstar	0.7079 mm	<0.001
Nidek OPD III	0.7158 mm	<0.001

The WTW between devices were correlated to that of Orbscan WTW using parametric tests of correlation (Pearson) and the correlation was found to be significant (Table 3).

Table 3: Shows the strength of correlation between the WTW of devices studied with that of Orbscan WTW

R Value	WTW Lenstar	WTW Galilei	WTW OPD III scan
WTW Orbscan	0.85	0.88	0.75

The ACD obtained using the devices used in the study were analysed (Table 4) and the impact of using the ACD from Lenstar, Galilei and Orbscan along with the WTW from the same machines on ICL sizing was studied.

Table 4: Comparison of ACD between the devices studied (Mean, SEM and 95% confidence intervals are mentioned)

Factor	Mean	Std. Error	95% CI
ACD Orbscan	3.1416	0.02501	3.0915 to 3.1918
ACD UBM	3.2716	0.02559	3.2203 to 3.3229
ACD Lenstar	3.6607	0.02544	3.6097 to 3.7117
ACD Galilei	3.7578	0.0246	3.7085 to 3.8071

When the ACDs of Lenstar and Galilei were used along with their respective WTWs, 20% and 10% of eyes respectively were two sizes

oversized compared to Orbscan sizing for the same eyes. These values are double of the percentages of two sizes oversizing when the ACD from Orbscan was used.

DISCUSSION

WTW and ACD are two important variables in the ICL size calculation and there are several machines which provide automated measurements of the same. Manual measurements are not as repeatable as automated measurements.[15]

The measurements of WTW and ACD have been compared between devices in a few studies. A comparative study between Pentacam and IOL master revealed that Pentacam measured significantly higher ACD and lesser WTW compared to IOL Master.[14]

A study by Salouti et al[12] showed that Orbscan WTW was significantly lesser in comparison to that of Pentacam and they should not be used interchangeably. Another study[13] by the same group has compared Orbscan with that of Eye Sys and Galilei systems and concluded that Orbscan WTW was significantly lesser than that of the other two and WTW of Galilei was closer to Orbscan WTW. Kiraly et al[16] among other devices compared Orbscan II WTW with that of IOL master and showed that Orbscan WTW was significantly lesser than IOL Master WTW.

The results of our study have been similar in that Orbscan WTW has been the least followed by Galilei, Lenstar and Nidek OPD III scan in the same order. There is no study till date which has suggested which among the devices is better for WTW measurement and how much these differences lead to a change in the ICL sizing.

In our study, the comparison of mean pre-operative predicted vaults with that of post-operative attained vaults revealed that among all the devices studied, Orbscan mean predicted vault was closest to the ideal vault suggesting the use of Orbscan WTW for better outcomes. A study by Cao et al using Orbscan had similarly good outcomes with vault in most of their patients.[17] When the sizing of ICL obtained with WTW from other devices were compared with the size that gave the patients a normal vault (calculated based on Orbscan WTW), we noticed that up to 20% patients would have been oversized by 2 sizes and another 50-60% by one size. This means that a significant number of patients would have had high vaults and possibility of complications had WTW been used from the other devices studied. This hypothetical ICL size calculation, when done also considering

the ACD derived from these devices instead of Orbscan ACD showed more oversizing than just considering their WTW along with Orbscan ACD.

This is the first study to show the rate of "significant oversizing of ICL size" with the differences in the WTW and ACD between the devices, which were known to occur even before.

In the current scenario where there is no clear protocol of using either the STS or WTW for ICL sizing and meta-analysis showing equivalent outcomes with the use of either of them, it becomes more important to understand the technical differences between the various machines derived WTW and ACD and how much of change they can lead to in the sizing of the ICL and in turn the vaulting.

CONCLUSION

This study conclusively proves that the WTW and ACD derived from the machines Orbscan, Galilei, Lenstar and Nidek OPD III scan are not at all interchangeable. The use of Orbscan WTW and ACD provided ideal mean predicted vaults and attained vaults in our patients and the hypothetical use of other machines can lead to a significant oversizing of the phakic intra ocular lenses and risk of complications. Correction factors are necessary to overcome this factor in order to attain vaults close to ideal vaults in our patients when using different devices for WTW/ACD measurements.

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Silicone Tube Loop Myopexy: Novel Surgical Modification Of Myopic Strabismus Fixus

Dr. Deepti P, Dr. Krishna Prasad R

ABSTRACT

PURPOSE

Loop myopexy of superior rectus with lateral rectus is a well established surgical treatment of myopic strabismus fixus. We evaluated safety profile and surgical outcomes of a novel modification of loop myopexy with silicon tube sling (used for ptosis surgery).

METHODS

It was a prospective interventional study. 19 eyes of ten patients with myopic strabismus fixus who presented to our OPD from January 2015 to June 2016 were surgically treated with silicone tube loop myopexy of superior rectus and lateral rectus. All eyes underwent additional medial rectus (MR) recession for varying grade. They were all followed up for 12 months post surgery. Pre and post operative horizontal deviation, vertical deviation and extraocular movements were recorded. Individual age, sex, duration of squint, visual acuity, refractive status, axial length, any previous squint operations, and associated complications were all noted. Myopic strabismus fixus due to causes other than myopia were excluded.

RESULTS

At the last follow-up,mean esotropia improved to 11.6+/-7.1 prism dioptre (PD) from 78.7=/-6.4 prism dioptre, p<0.001; deviation

≤ 20 PD was achieved in to be filled in 73.68 % eyes. Mean hypotropia at presentation was 13.4=/-10.3 which improved to 1.3=/-2.3 prism diopter post-operative, $p < 0.001$. There was a significant improvement in ocular motility, $p < 0.001$.

CONCLUSION

Modified silicone tube loop myopexy with or without MR recession is a safe, easy and effective procedure in the management of myopic strabismus fixus and improves alignment significantly. Efficacy is comparable with other methods of loop myopexy. No significant complications noted.

KEY WORDS

Myopic strabismus fixus, esotropia- hypotropia, silicon tube loop myopexy

INTRODUCTION

Myopic strabismus fixus, or heavy eye syndrome, is an adult onset esotropia associated with high axial myopia, typically described as progressive esotropia and hypotropia associated with restricted elevation and abduction of variable degree and severity. According to studies,[1,2] there is superotemporal herniation of the posterior portion of the elongated globe from the muscle cone due to increased axial length. Therefore, the lateral rectus(LR) muscle is displaced inferiorly and superior rectus (SR) muscle is displaced nasally, resulting in limitation or failure to abduct and elevate.

Loop myopexy of superior and lateral rectus has become the standard procedure of choice for myopic strabismus fixus. Various techniques of loop myopexy including sutures[3] and silicon bands[4,5] have been advocated in past. The disadvantage of suture myopexy includes muscle strangulation, which may affect anterior ciliary circulation and may rarely cause cheese-wiring of the muscle.

We performed a novel modification loop myopexy using silicon tube which has been used for performing ptosis surgery. Being thinner, circular and hence absence of indentation or pressure points, need for lesser tissue handling and smaller scleral tunnel for fixation gives the primary advantage of using a silicon tube over a silicon band.

MATERIALS AND METHODS

Objective

To evaluate safety profile and surgical outcomes of a novel modification of loop myopexy with silicon tube sling (used for ptosis surgery) for patients with myopic strabismus fixus.

Materials and methods

This is a prospective interventional case series of nineteen eyes of ten patients who had underwent silicon tube loop myopexy of superior rectus and lateral rectus for myopic strabismus fixus at a tertiary eye care centre, South India from January 2015 to June 2016. All the surgeries had been performed by the same team of surgeons. This study was approved by ethics committee and the study was carried out in accordance with the approved guidelines. Informed consent was obtained from all subjects before surgery.

In our study, all patients were diagnosed to have myopic strabismus fixus preoperatively and was confirmed by computed tomography of orbit and brain, showing superotemporal herniation of the elongated eyeball from the muscle cone, inferior displacement of the LR, and nasal displacement of the SR. Other intracranial related pathologies are excluded. Patients with less than 6 months follow-up were excluded.

The degree of esotropia and hypotropia was assessed preoperatively and postoperatively for each patient by prism bar cover test (PBCT). In the situation that PBCT could not be performed due to extreme limitation of extraocular muscle movement, the degree of ocular deviation was estimated by the Krimsky test.[6,7] The degree of restriction of extraocular movement was graded into 3 grades of impairment. Grade 0 is no restriction, grade 1 is mild restriction where eyes cross midline; Grade 2 is moderate restriction in which the eye could not cross midline; Grade 3 is extreme restriction with the eye fixed in adduction with minimal movement. The degrees of restriction are reported preoperatively and postoperatively.

Individual age, sex, duration of squint, visual acuity, refractive status, axial length, any previous squint operations, and associated complications are all reported.

Surgical Techniques

All patients had surgery under peribulbar anesthesia. Forced duction

tests were performed to confirm the restriction. Silicon tube loop myopexy of SR and LR was performed for all patients as described below.

A forniceal conjunctival incision is created in the superotemporal quadrant approximately 8 mm posterior to the limbus. LR and SR muscles are then identified and isolated. About 14 mm from limbus scleral tunnel was made. Silicon tube was passed below LR, through the scleral tunnel and then below SR. While insertion of tube below the muscle, the needle was folded over the tube and the base of needle was passed below the muscle, taking care not to injure muscle with needle. The tube was then passed through the sleeve and secured (Figure 1). In cases where scleral thinning prevented us from making a scleral tunnel, the tube was secured 14 mm beyond the limbus to the sclera by using 5-0 ethibond suture. All eyes underwent medial rectus recession in same sitting.

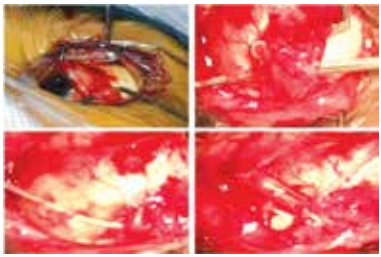

Fig.1: Surgery for loop myopexy. From left to right- A- demonstration of displaced muscles. B- insertion of tube beneath muscle. C- scleral fixation of the tube. D- loopmyopexy of SR and LR with tube secured with sleeve.

RESULTS

19 eyes of 10 patients were recruited in the study. Majority of subjects were males (73.7%) and 26.3% were females. Age ranged from 17 to 74 year old, mean age of subjects in the study was 54.9 ± 15.8 years. All patients were followed up for a period of 1 year.

Characteristics of operated eyes

Best Snellen Corrected Visual Acuity of the operated eyes ranged from hand movement to 0.25, mean BCVA was 0.1 ± 0.1. Axial length of the operated eyes ranged from 27 mm to 35.98 mm, with a mean of 31.4 ± 2.7 mm. The spherical equivalent of the refractive error of the operated eyes ranged from −10.00 D to −24.50 D mean being 17.4 ± 3.4 dioptres. Only one patient had previous history of surgery-medial rectus recession and lateral rectus resection performed.

Loop myopexy surgery

In this series, 9 patients underwent bilateral loop myopexy whereas 1 patient underwent unilateral loop myopexy. Totally, 19 eyes

underwent additional MR muscle recession. Mean pre-operative horizontal deviation at baseline was 78.7 ± 6.4 prism dioptres and at post surgery 3 months was 11.6 ± 7.1 prism dioptre. There was significant decrease in mean horizontal deviation at all the post-operative period compared to pre-operative horizontal deviation, $p<0.001$. A significant decrease in mean vertical deviation from 13.4 ± 10.3 prism diopter preoperative to 1.3 ± 2.3 post-operative 3 months was noted, $p<0.001$. From preoperative to post operative 3 months, there was a significant improvement in grade of extraocular movements compared to baseline Grade, $p<0.001$.

DISCUSSION

Silicon tube loop myopexy of superior rectus and lateral rectus is an effective treatment for patients with myopic strabismus fixus as it can reduce the degree of esotropia and increase in range of extraocular movement by a significant amount. As proposed by Kekunayya et al,[5] the surgery helps to normalize the vectors of muscle force of the superior rectus and lateral rectus, allowing the globe to move more freely within the muscle cone by eliminating the mechanical disturbance of eye movement.

In our study we performed silicon tube loop myopexy of 19 eyes. In addition, we did do a variable amount of recession of medial rectus in all our patients as just a loop myopexy did produce residual esotropia in few of our patients. In patients with noted fibrosis of medial rectus, a hang back recession of medial rectus was performed. There was a significant decrease in horizontal and vertical deviation post operatively. The improvement in the grade of extraocular movements was also significant (Figure 2). No significant complications were noted post

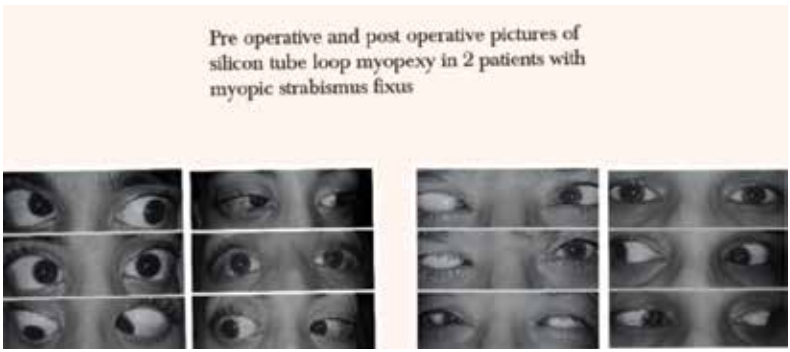

Fig. 2: Pre operative and post operative pictures of patient post silicon tube loop myopexy.

operatively. One patient did complain of chronic foreign body sensation, but that could be explained by anterior placement of loop. As the complaint was nonspecific, no further intervention was performed.

As compared to suture myopexy,[3,8] the chances of cheese wiring of muscles and anterior segment ischemia was eliminated. Moreover silicon tube loop myopexy is reversible.

Silicon tube (which is commonly used in ptosis surgery) in comparison to silicon bands which have been used previously for loop myopexy,[4,5] is thinner and circular (Figure 3). Hence, there is an absence of indentation or pressure points on sclera. It also warrants a need for lesser tissue handling and a smaller scleral tunnel for scleral fixation.

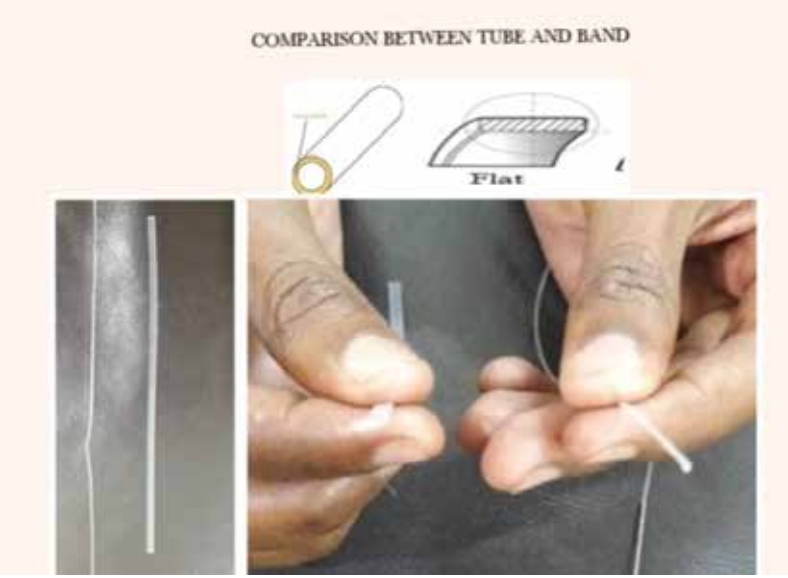

Fig. 3: Comparison between silicon tube and band.

The major drawback of the study is smaller sample size. As myopic strabismus fixus is a rare ocular condition, the sample size is justified.

CONCLUSION

Modified silicone tube loop myopexy with or without MR recession is a safe, easy and effective procedure in the management of myopic strabismus fixus and improves alignment significantly. Efficacy is comparable with other methods of loop myopexy. No significant complications noted.

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The Claw- A Novel Intraocular Foreign Body Removal Forceps

Dr. Maneesh Bapaye, Dr. Mahesh P. Shanmugam, Prof. Dr. S. Natarajan

Penetrating ocular injuries are associated with retained intraocular foreign body (IOFB) in 17-41%[1] of patients. It is an important cause

of visual morbidity and blindness especially in working age population. In majority of patients the IOFB is retained in posterior segment of the eye. Three port pars plana vitrectomy with internal removal of IOFB is a standard procedure for removal of posterior segment IOFB. Advent of small gauge vitrectomy has lead to excellent visual and anatomical outcomes in majority of cases. While various instruments like intraocular foreign body magnets and various types of forceps have been successfully used for removal of IOFB, removal of large, spherical, non magnetic IOFBs like shot gun pellets, stones or large glass fragments remains challenging in majority of cases. We introduce a new device that can be used in such cases successfully.

DESCRIPTION OF INSTRUMENT

The Claw (Fig.1) is an extendable foreign body forceps (Epsilon, USA). It is designed for secure grasping and removal of large, non magnetic foreign bodies from vitreous cavity. The instrument consists of titanium handle and 19 G stainless steel shaft. A Teflon plunger is housed inside the titanium handle. To and fro movement of the plunger is controlled by a screw shaped knob placed at center of the shaft. When deployed the plunger pushes the claw shaped prongs housed inside the stainless steel shaft in a symmetrical manner. The stainless steel shaft has outer diameter of 1.2 mm and inner diameter of 0.9 mm. Length of the shaft is 27 mm.The retractable claw is made of 4 prongs of Nitinol wire. Nitinol is alloy of nickel and titanium which shows excellent shape memory and psuedoelasticity. Because of its biocompatible nature Nitinol is widely used in many medical devices. When completely extended the prongs measure 14 mm and

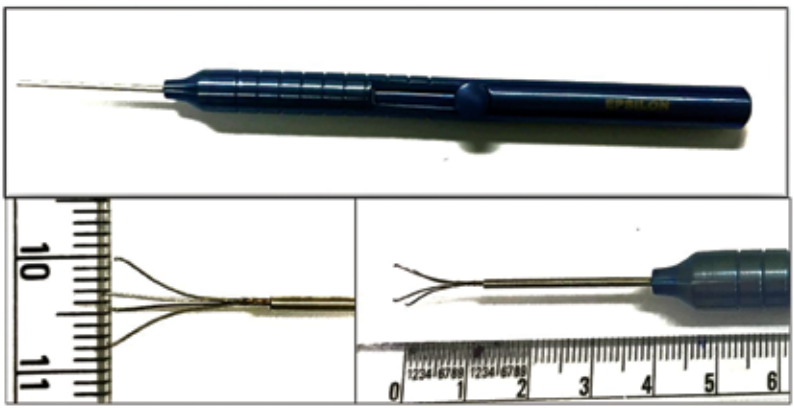

Fig. 1: The Claw

open up to 8-8.5 mm. The prongs are retracted fully into metallic cylinder while introducing in the eye. Conjunctival opening and enlargement of sclerotomy is needed to introduce the forceps in vitreous cavity. The distal ends of the prongs are bulbous and hence non-traumatic to the retina. Forceps can be held by comfortable grip while prongs can be extended or retracted to extent required with the knob using one of the fingers. Once IOFB is grasped in the prongs of the claw are retracted to hold the IOFB in-situ. The prongs twine around the IOFB to hold it secured manner. The forceps can be reused after autoclave.

The Claw has been used by surgeons for removal of various large and non magnetic IOFBs in different clinical settings.

Clinical Scenario 1

A 42 year old male presented with history of penetrating trauma in right eye while standing beside a stone cutter. At presentation visual acuity was no light perception. Clinical examination revealed scleral tear on nasal side. Posterior extent could not be ascertained. Cornea was clear. Hyphema precluded view of fundus. Eyeball appeared collapsed. CT scan examination showed a large radio-opaque IOFB with collapsed eyeball (Fig 2). Surgery was planned for wound exploration and suturing and removal of IOFB to prevent traumatic endophthalmitis. Intraoperatively scleral wound was explored to the posterior extent after disinsertion of medial rectus muscle and sutured with 6-0 vicryl suture with hand over hand technique. Lensectomy was performed through limbus. Standard 3 port pars plana vitrectomy performed with 23G TSV system. A large stone IOFB along with total RD and vitreous hemorrhage were noted. Posterior vitreous detachment was absent. IOFB was released of all vitreous attachments and IOFB was lifted to papillary plane using the Claw (Fig 3). Superior 180

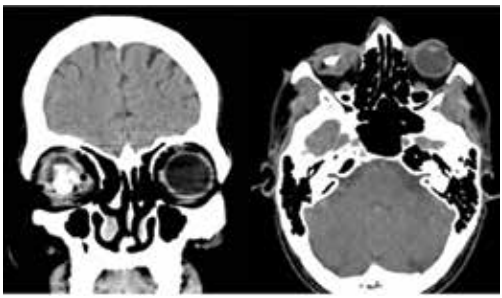

Fig.2: SCT scan images showing deformed eyeball with large IOFB

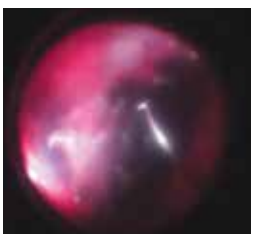

Fig.3: Large IOFB (Stone) being held in mid vitreous cavity using the claw

degrees limbal section was made and IOFB removed with superior rectus holding forceps by handshake technique. It measured 10 mm X 5 mmX 4 mm (Fig 4).

Fig.4: Composite depicting size of IOFB

Clinical Scenario 2

In July 2016, Kashmir valley erupted with social unrest of unprecedented proportions. Extensive stone pelting was resorted to by unruly crowds. Security forces were forced to use pellet guns for crowd control. However this resulted in extensive ocular injuries. Over 2000 subjects suffered pellet injuries. Of these 855 had ocular injuries. 118 patients had posterior segment IOFBs.

The pellet gun is technically known as 12 bore pump action gun. These guns are manufactured at ordinance factory at Ishapore, West Bengal. A cartridge of pellet gun contains several hundred pellets which spread over a large area once fired. Cartridges which contain pellets or shots of various sizes measured on scale BB and 1-9. Pellets are marked as BB are largest in size, shot no.1 is smaller than shot BB and shot no. 9 is the smallest of all. The size of these pellets varies from 2.03 mm (Size 9) to 4.57 mm (Size BB). The pellets are made of lead, usually spherical in shape and have smooth surface, resembling ball bearings. It makes them difficult to remove from eye. The 'Claw' was used to remove these IOFBs (Fig.5). Two of the authors, Drs. SN and MPS were surgeons in-charge of operating on these patients.

The Claw has also been used in vivo to pick up various objects like large glass pieces without crushing them into smaller splinters (Fig. 6)

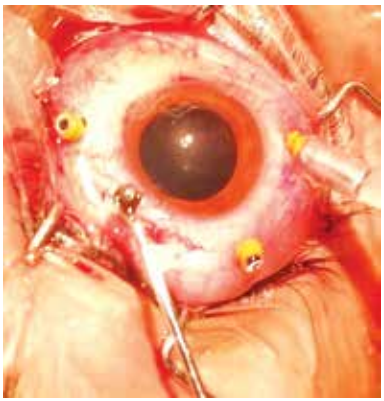

Fig. 5: Shotgun pellet after removal from eye

Fig. 6: Irregular shaped glass piece held in-vivo

DISCUSSION

Removal of IOFB in setting of penetrating trauma is challenging scenario. In majority of cases the IOFBs are small in size and magnetic in nature, which makes removal of these IOFB amenable to magnets for removal. However when IOFB is non-magnetic and/or large in size (4 mm or more), there are limited options available for holding the IOFB securely inside the vitreous cavity.

The instrument design was based on concept of dormia basket that has been extensively used in urology for removal of proximal ureteric stones. The dormia basket consists of retractable basket of nitinol cables which is passed beyond the ureteric stone in retracted state and then deployed while it is pulled out so as to catch the stone within the basket and then removed. Similar principle is also used in sialo endoscopy for removal of salivary stones. We started by working with design concept of a retractable nitinol basket. In case of IOFBs in ocular trauma, the major differences from prior mentioned applications of basket design are variability in shape of IOFBs rather than spherical shape of ureteric or salivary stone. The IOFBs are lying on relatively flat surface rather than tubular lumen and can potentially float in liquid environment of vitrectomised eye prior to removal. Claw design was used as it enables the surgeon to hold the IOFB securely by approaching in antero-posterior direction and picking it up from retinal surface.

Various authors have described snare or loop design that can hold an irregular IOFB. Erkagun et al[2] and Murthy et al[3] have described

cost effective and disposable snares using thick suture materials, which can be quickly assembled prior to surgery and disposed off once used. Eckardt C et al[4] (Memory snare IOFB Extractor; DORC, Zuidland, Holland) and Smith JM et al[5] (QuikStik; Microsurgical technology, Redmond WA) have described expandable memory loop devices which contain expandable nitinol loop. While all these elegant devices can be effectively used linear IOFB, it is difficult to hold larger and spherical IOFB. Snare design devices can cause repeated slippage of IOFB. Iatrogenic trauma by slipped IOFB can lead to less than satisfactory anatomical and visual outcomes, especially if macular region is affected.

Different types of forceps have also been used in these cases with large IOFBs. Hickinbotham D et al[6] have described diamond coated forceps to hold IOFB in vitreous cavity. However the opening of prongs is not quite as wide to hold large IOFB and presence of 2 prongs makes removal of spherical IOFB difficult. Liang S et al[7] have used micro-alligator forceps for removal of large IOFB. To introduce this forceps needs very large sclerotomy. Crushing force of forceps can also be significant leading to crushing or splintering of the IOFB prior to removal. This may further complicate the situation for the surgeon. McCarthy M.J. et al[8] have used ureter stone forceps itself. This has very large handle and needs assistant to operate the instrument.

The claw offers various advantages over all of the aforementioned devices. The 4 prongs offer secure grip without crushing or splintering the IOFB. As mentioned before, the IOFB can be approached in antero-posterior direction and picked up from flat retinal surface. Chances of IOFB slippage and thereby causing retinal trauma are minimized. It makes other procedures like creating limbal incision or enlargement of sclerotomy with other hand while FB is securely held with one hand in mid-vitreous cavity or at the pupillary plane. The forceps can be sterilized with standard methods and thus reusable and cost effective option. Design of 4 pronged claw shaped disposable forceps has been described by Hildebrandt C el al[9] of University of Wisconsin, Madison as a part of term project for biomedical engineering course. However in their instrument, which was a prototype, the claws couldn't be retracted fully in metallic cylinder. This instrument was never used in human subjects.

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Clinical Profile Of Uveitis In Treated, Histopathologically Negative Hansen's Disease

Dr. Radha K Annamalai, Dr. Muthayya Muthukumar

PURPOSE

The primary objective is to identify the type and clinical nature of uveitis in Hansen's disease after treatment is completed and is proven to be negative on histopathological examination of skin biopsy.

METHODS

A prospective cohort study conducted over 3 years on of 120 patients who had completed treatment for Hansen's disease. Complete

ophthalmic evaluation, PCR and RT- PCR was done on aqueous humor samples. Chi square analysis was performed. This is a prospective study performed in a tertiary referral hospital in India. It was performed after institutional ethics committee approval and an informed consent was obtained from all patients. Inclusion criteria comprised of all patients with Hansen's disease who had completed treatment for either paucibacillary, multibacillary or indeterminate type of leprosy. Patients who had not completed treatment and those with other forms of systemic infections such as tuberculosis, toxocariasis, candida retinochoroiditis were excluded from the study. All cases were referred from a leprosy rehabilitation centre in Chennai, Tamilnadu and the study was conducted in concurrence with the department of dermatology. Other criteria for enrolment in the study were, adequate follow-up for atleast one year from the onset of uveitis and completeness of the medical and ocular records. The ocular examination included a visual acuity examination, slit-lamp examination, applanation tonometry, corneal sensation and Schirmer's tests. The treatment for multibacillary leprosy was a standard regimen for 12 months consisting of rifampicin 600 mg once a month, dapsone 100 mg daily and clofazamine 300 mg once a month. Those with paucibacillary leprosy had completed a regimen of 6 months duration which included rifampicin 600 mg once a month and dapsone 100 mg daily. Management of uveitis was done using topical cycloplegics and corticosteroid eye drops to manage inflammation. A split skin microscopy was performed in each patient to confirm the activity of the disease, the extent of systemic disease and the response to treatment. The smear estimated the number of acid-fast bacilli that were detected and this was reported as the bacterial Index. Skin smears were taken from earlobes, elbows and knees as well as from lesions in the patient. AC paracentesis was performed under aseptic precautions using povidone iodine and a 26 gauge needle mounted on a tuberculin syringe. 0.1 ml of aqueous humour sample was obtained. Ziehl Neelson Carbol Fuschin stain was used for the diagnosis after the slide was prepared. In those with recalcitrant uveitis, a polymerase chain reaction (PCR) was performed on the aqueous humor sample. The sequences that were targeted using PCR included genes encoding the DNA of 36-kDa antigen, 18-kDa antigen, 65-kDa antigen and the repetitive sequences among other M. leprae genes. RT- PCR was performed based on response to uveitis and the aqueous humor sample of 3 patients was analysed for pathogen. Apart from genetic sequencing, complete blood counts, purified protein tests and chest x rays were done for

all patients. Follow up was done for 3 years and during each visit a complete ophthalmic evaluation was performed.

RESULTS

Incidence of uveitis was 39% with blindness in 9% which was reversible in 6%.This study was performed on 120 eyes of 90 patients with uveitis over a three year period. Ages ranged from 25 to 60 years. Acute anterior uveitis was seen in 28% and chronic in 72%. 43%

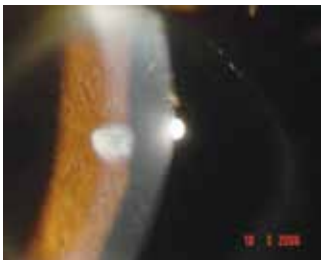

Fig. 1: Mutton fat keratic precipitates and iris pearls

Fig. 2: Complicated cataract in chronic uveitis

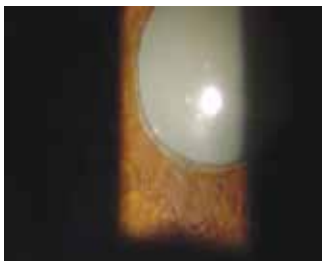

Fig. 3: Iris sphincter atrophy with dilated pupil

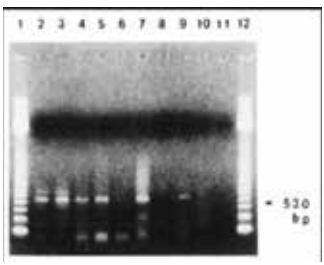

Fig. 4: PCR detection of M. leprae DNA from aqueous humor samples

Fig. 5: Smear made from anterior chamber aspirate shows granular beaded dead bacilli and fully formed live bacilli coexisting in the same patient. Zeihl- Neelson x 790

were lepromatous, 12% indeterminate and 45% tuberculoid leprosy. RT- PCR detected live bacilli in tuberculoid leprosy.

38% showed acute anterior uveitis and 62% showed chronic anterior uveitis. It was granulomatous in 83% with the predominant clinical feature being iris sphincter atrophy and dilated pupil with large mutton keratic precipitates and anterior chamber cells and flare.

17% of patients presented with a non- granulomatous iridocyclitis although that is not a usual presentation in uveitis. Cataract was noted in 33% of patients. On morphological evaluation, posterior subcapsular cataract was the most common feature and both senile and complicated cataract were seen. Several of our patients had dilated pupil due to iris sphincter atrophy. Vitritis was present in 3% of patients and was seen as grade 2 cells with vitreous haze. Fundus examination was normal in all patients. 12% of patients had scleritis of the nodular type. Those with scleritis showed resolution with topical steroids with no recurrence and a scraping was not performed on them. Treatment for iridocyclitis was 1% atropine eye drops, 1% prednisolone acetate eye drops and oral steroids in the dose of 1mg per kg body weight. In those with no resolution to this treatment for more than 3 weeks, an anterior chamber paracentesis was performed. RT- PCR performed on the aqueous humour of 12 patients with recalcitrant uveitis showed detection of DNA of M. leprae in 3 of them. A smear in these patients showed the presence of live and dead bacilli. Microscopy showed the typical morphology of fully formed live bacillus and beaded dead bacilli both existing in the same sample. After completion of treatment, the onset of uveitis in the paucibacillary type occurred within 1 year in 9% of patients, 2 years in 33% and within 3 years in 11%. Those with multibacillary leprosy had recurrence of uveitis after 3 years of completion of treatment. No patients had uveitis before that time period.

CONCLUSION

Acute anterior uveitis in leprosy is more common in the tuberculoid type despite completion of treatment. RT- PCR on aqueous is useful in chronic uveitis and requires ocular follow up even if histopathology is negative for the bacillus. Evaluation and analysis of aqueous humour by PCR has shown that DNA assays can be very sensitive in identifying bacilli and their DNA. Patients who have completed treatment are more likely to have persisting M. leprae bacilli in the aqueous humour in the paucibacillary type. Also the recurrence of uveitis is earlier in these patients than the multibacillary type. We found in our study that the commonest cause of defective vision is chronic uveitis with complicated cataract which is treatable if detected early. It may be required to start anti leprosy treatment again when live bacilli are seen in the aqueous humour even if the systemic status has settled. PCR can certainly ascertain the diagnosis by detecting even few bacilli from a small sample. This may actually be helpful in breaking the chain of leprosy transmission. PCR of aqueous humour can be adopted

as a routine in all patients who present with anterior uveitis after completion of leprosy treatment. The prevalence of uveitis and blindness in leprosy can vary between different populations. A programme for screening of leprosy should continue throughout the course of treatment and at regular intervals even after completion of treatment for both multibacillary and paucibacillary forms.

INFERENCES

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2. It is more common in the tuberculoid variety
3. Longer duration of treatment may be required though it is paucibacillary type
4. Recurrence of uveitis is earlier and more frequent in this type
5. Middle aged and elderly develop more severe uveitis

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Clinical Presentation, Management And Visual Outcomes Of Pediatric Sympathetic Ophthalmia At A Tertiary Eye Care Center In South India

Dr. Saurabh Mistry, Dr. Parthopratim Dutta Majumder, Dr. Jyotirmay Biswas

ABSTRACT

PURPOSE

To study the clinical presentation and visual outcome of sympathetic ophthalmia (SO) in pediatric patients attending a tertiary care center.

METHODS

Retrospective review of patient's ≤ 18 years with sympathetic ophthalmia seen during the period 1997–2017.

RESULTS

17 patients were included. The inciting event was trauma in 13 patients whereas 4 patients developed SO following vitrectomy. The commonest presenting signs were anterior uveitis and exudative detachment. All patients were treated with systemic steroids, while 14 patients received additional immunosuppressive therapy. Of these, 4 patients needed more than one IMT drug to control the inflammation. 14 patients had a follow-up of more than 6 months. 4 patients developed recurrence on follow-up. The most common complication on long term followup was complicated cataract (9 patients) and secondary glaucoma (6 patients). Mean presenting best-corrected visual acuity (0.75 ± 0.60 logMAR) in the sympathizing eye improved significantly following treatment (0.26 ± 0.36 logMAR).

CONCLUSIONS

Appropriate immunosuppression can lead to favourable visual outcomes in the sympathizing eye of pediatric patients.

KEY WORDS

Sympathetic Ophthalmia, Pediatric group, Imunosuppressives

INTRODUCTION

Childhood blindness continues to be one of the major public health problems in developing countries. It is estimated that there are 1.4 million blind children in the world, two thirds of whom live in the developing countries, and that the causes of blindness in children vary according to region and socioeconomic development.[1,2] Childhood blindness, especially if it is avoidable, is a particularly emotive subject more so, because of its significant impact on the child's development, education, future job opportunities and quality of life.[3] A recent survey of childhood monocular blindness in a rural population in southern India found ocular trauma to be the second leading cause (the first being amblyopia due to uncorrected refractive errors) of visual impairment in the pediatric age group.[4]

Saxena et al. studied the pattern of ocular trauma in pediatric age group. They found that closed globe injuries accounted for 42.2% injuries, open globe for 53.9% whereas 3.9% were due to chemical injuries. Most common cause of injury was bow and arrow (15.2%) followed by house hold appliances (14.3%). Also, best corrected visual acuity of 6/12 or better was achieved in 79 eyes (91.86%) in closed globe group. However, only 17 eyes (15.45%) in open globe group could achieve this.[5] Penetrating injuries or open globe injuries have a higher risk of blindness not only from immediate ocular damage but also from long-term complications like sympathetic ophthalmia (SO).

SO is a bilateral diffuse granulomatous panuveitis that occurs after accidental or surgical insult to the uvea of one eye. After injury from either surgery or accident, a variable period of time passes before a sight threatening inflammation develops in both the eyes. The incidence of SO ranges from 0.2 to 0.5% after penetrating ocular injuries and 0.01% after intraocular surgery.[11,12] The disease usually responds rapidly to corticosteroid therapy, but recalcitrant cases may require the addition of other immunosuppressive agents. A severely injured eye with no prognosis for vision should be enucleated within 2 weeks of injury to prevent SO.

Recently, Kumar et al estimated the incidence of SO following trauma. It was 0.24% in the pediatric age group.[6] Though quite less, this complication assumes paramount significance because of its potential to cause blindness in both eyes following an injury to one eye. Recognition of signs and symptoms of SO is thus important because the disease is vision threatening and many patients may end up with significant vision loss especially if treatment is not started quickly. Also, it is particularly challenging to manage pediatric patients, with very scanty literature available regarding management guidelines in such cases.

The current study was undertaken to look into the data of last 20 years' in another tertiary eye care centre in Southern India. To the best of our knowledge the current study is the largest case series on pediatric SO from India.

METHODS

This was a hospital-based retrospective case series that reviewed the files of all consecutive patients with SO at a single tertiary center between December 1997 and January 2017. The patients ≤ 18 years

receiving a diagnosis of SO were included in current study. Cases with insufficient documentation and inadequate follow-up was excluded from the study.

All patients underwent detailed medical evaluation, including medical history, best corrected visual acuity (BCVA), visual field assessment, slit lamp microscopy, intraocular pressure (IOP) by applanation tonometry, and indirect ophthalmoscopy. All the patients underwent FFA, USG and OCT in sympathizing eye and in case of an uncertain clinical picture, patients underwent ICG.

SO was diagnosed on the basis of two or more signs in sympathizing eye, with history of trauma or surgery preceding the onset of intraocular inflammation in other eye.[6,9]

1. Anterior segment inflammation
2. Posterior segment showing vitritis, exudative retinal detachment, optic nerve head edema, nummular chorioretinal lesions, vasculitis or a sunset-glow fundus.
3. Diffuse choroidal thickening in the posterior pole on B-scan ultrasonography (USG)
4. Multiple pinhead leak with late dye pooling, optic nerve head staining on fundus fluorescein angiography (FFA) and/or suggestive indocyanine green angiography (ICG) and/or multiple serous retinal detachment on optical coherence tomography (OCT)
5. Characteristic histopathology of the enucleated exciting eye

The data including sex, age, clinical presentation, ocular involvement, type of ocular injury, time of injury, time from first injury to development of disease and to presentation were entered into a computer database. Visual outcome and subsequent incidence of ocular complications such as cataract, ocular hypertension, hypotony, macular edema, choroidal neovascularization, subretinal fibrosis, retinal detachment were also recorded.

BCVA results were converted to logarithm of the minimal angle of resolution (logMAR) for statistical analysis and are presented as logMAR and Snellen equivalent. Decrease in visual acuity was defined as two-step decrease in BCVA in Snellen's chart. Ocular hypertension was defined as an IOP greater than 21 mmHg and ocular hypotony was defined as IOP less than 6 mmHg. Uveitis was classified according

to the Standardization of Uveitis Nomenclature (SUN) Working Group classification.[10]

All statistical analyses were performed using SPSS (SPSS Inc, Chicago, Illinois, USA) statistical package. The statistical analysis was performed using SPSS 14.0 and any statistical tests with p value less than 0.05 was considered as statistically significant. Descriptive statistics was used for continuous variables and frequency distribution was used to determine the distribution of qualitative variables. Wilcoxon signed rank test was used to determine the difference between pre treatment and final visit visual acuity.

RESULTS

From December 1997 to January 2017, 17 patients ≤ 18 years of age with the diagnosis of SO were seen in our center. Eleven patients (64.7%) were male and six (35.3%) were female. The mean age at presentation was 11.1 ± 3.1 years (range: 5 – 17 years). The inciting event of SO in 15 patients was penetrating trauma, whereas 2 patients (developed SO following vitrectomy. The median time from initial injury to onset symptoms of SO was 59 days (range: 10 to 1215 days).

Average duration of follow-up was 58 months (range, 1.4 – 224.4 months).

The commonest presenting signs were anterior uveitis, exudative detachment and disc hyperemia.

Mean presenting BCVA in the exciting eye was 3.12 ± 1.25 logMAR units (median visual acuity PL +ve). 5 exciting eyes subsequently developed phthisis during the course of follow-up. 2 exciting eyes developed band shaped keratopathy on follow-up.

Mean presenting BCVA in the sympathizing eye was 0.75 ± 0.60 logMAR units (median visual acuity 6/36). 6 patients had visual acuity of 20/200 or worse. The most common complication on long term follow up was complicated cataract (9 patients), secondary glaucoma (6 patients) and subretinal fibrosis (3 patients).

Management

All 17 patients received systemic steroids, with 6 patients receiving additional intravenous methylprednisolone at presentation. Immunosuppressives were concurrently started in 14 patients (82.35%), of these 4 patients needed more than one immunosuppressant drug to control the inflammation.

The commonly preferred first line immunosuppressant drug was azathioprine and the second line drug was cyclosporine in our patients. The average duration of immunosuppression required to control inflammation was 7.85 months (range, 2.5 to 22 months).

Recurrence of symptoms in sympathizing eye was noticed in 4 patients during the course of follow-up. Of these, one patient was not started on immunosuppressive therapy during the initial presentation.

Lensectomy with pars plana vitrectomy was performed in 3 sympathizing eyes during the course of the follow-up. Trabeculectomy to control secondary glaucoma was needed in one of the sympathizing eyes.

1 exciting eye underwent evisceration during the follow-up. Histopathological report suggested no granulomatous inflammation, and few chronic inflammatory cells. 1 exciting eye underwent enucleation and histopathological report suggested chronic granulomatous inflammation involving retina and choroid consistent with diagnosis SO.

Mean final BCVA in the sympathizing eye was 0.26 ± 0.36 logMAR units (median visual acuity 6/9), which was significantly better than the presenting visual acuity with p value =0.038 using Wilcoxon signed rank test. [Figure 1] Good outcome (6/12 or better) was seen in 70.58% eyes (12/17), while 2 eye had fair outcome (6/12 to 6/60).

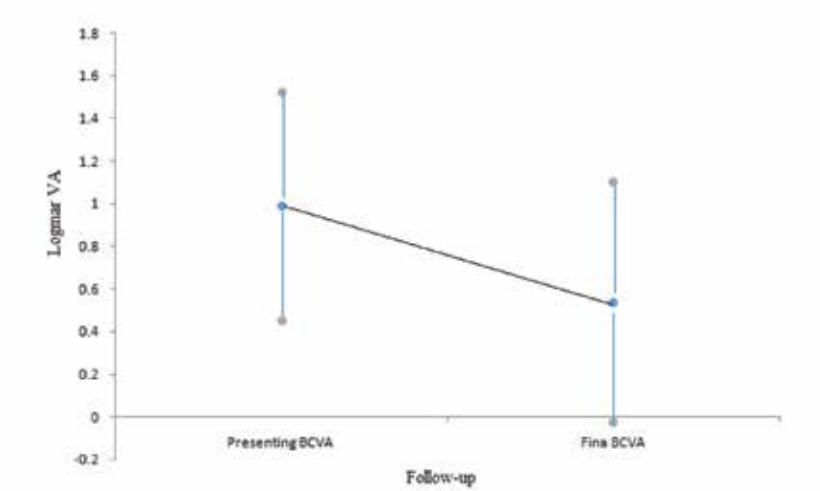

Fig. 1: Visual Outcome in Sympathizing eye: Mean plot with 95% CI showing significant difference between presenting and final BCVA. Wilcoxon signed rank test ($p = 0.038 < 0.05$).

Three sympathizing eyes had poor visual outcomes (>6/60 snellen VA). Of these, one eye had poor visual outcome due to development of secondary glaucoma and subsequently patient underwent trabeculectomy to control the intraocular pressure. One patient had presented to our OPD almost after 3.5 years (1215 days exactly) after the initial inciting event, with presence of extensive subretinal fibrosis in the sympathizing eye. Third patient had multiple episodes of disease recurrence with complicated cataract and BSK at initial presentation.

Mean final BCVA in the exciting eye was 2.84 ± 1.49 logMAR units (median visual acuity PL +ve). 3 exciting eyes had very good improvement in visual acuity 6/12 or better at final follow-up.

DISCUSSION

The patients in the current series developed SO following injury by a variety of mechanisms. This is consistent with the literature, where studies have reported sympathetic ophthalmia following trauma to be most likely cause. In our series, the commonest object causing trauma was wooden stick (23.5%). These findings correlate well with various studies done in India.[13,14]

However, more recent studies report injury from ocular surgery to be the more common cause.[15] Although incidence of sympathetic ophthalmia has declined in the recent past, prevalence of ocular surgery is increasing and necessitates careful monitoring of changing disease incidence. Sympathetic ophthalmia is a concern following multiple intraocular surgeries such as cataract extraction, paracentesis, and iridectomy, and is of particular concern following vitreoretinal surgery.

Vitreoretinal surgery is suggested to be the cause behind half of all sympathetic ophthalmia cases and, thus, upto 1 out of every 800 vitreoretinal cases.[16] Interestingly, in our case series two patients presented with SO following multiple vitreo-retinal surgeries after penetrating trauma and one patient following vitrectomy alone without any antecedent trauma. Performing multiple vitreo-retinal surgeries in a traumatized eye with poor visual prognosis may further increase the risks for developing SO in such eyes.

Our data showed that most of the patients (65%) developed SO within 2 months following the initial injury (median interval of 54 days).

Table 1: Characteristics of the study population with sympathetic ophthalmia

Sl. No.	Age (yrs)	Time from injury to onset of symptoms (days)	Mode of injury	Sympa-thizing eye	Presenting Visual acuity (logMAR)-OD; OS16	Mode of treatment	Duation of IMT (days)	Recurrence	Final visit visual acuity (logMAR) – OD; OS	Follow-up duration (days)	Comp-lications in sympa-thizing eye
1	11	24	Metal Rod, S/P Vitrectomy	OD	0.2;0.48	CS+IMT(1)	75	No	0.0;4.0	1439	Cataract
2	7	38	Details of Trauma NA	OD	0.2;3.5	CS+IMT (1)	210	No	0.0;0.3	812	Glaucoma
3	14	1095	Trauma with stick	OD	1.0;4.0	CS+IMT (3)	540	Yes (1)	3.5;4.0	1813	Cataract; Glaucoma; Subretinal fibrosis
4	10	15	Fist injury	OS	3.5;3.0	CS+IMT(1)	480	Yes (2)	4.0;2.77	6320	Cataract
5	15	10	Hit by Stone	OS	3.5;0.0	CS	NA	No	4.0;0.0	6732	Nil
6	15	66	Chisel & Hammer	OD	3.5;3.5	CS+IMT(1)	660	No	0.1;4.0	5648	Cataract; Glaucoma; RD
7	8	40	Injury with hair band	OS	0.0;0.6	CS	NA	No	0.0;0.2	1710	Nil
8	12	240	Details of trauma NA, S/P PK	OD	1.0;1.0	CS+IMT (1)	120	No	0.0;2.77	830	Cataract; Glaucoma

9	13	1095	Injury with rubber baloon	OS	3.0;1.0	CS	NA	Yes (1)	3;0.18	2660	Cataract; Glaucoma
10	12	545	Trauma with stick; S/P Cataract Sx	OD	0.18;2.0	CS+IMT (1)	115	No	0.0;2.0	400	Nil
11	9	47	Trauma with aluminium plate	OD	0.48;0.48	CS+IMT(2)	150 and ongoing	No	1.0;1.0	155	Cataract
12	11	59	Trauma with stick; S/P Vitrectomy	OS	3.5;0.3	CS+IMT(1)	120	No	4.0;0.0	125	Nil
13	9	50	Trauma with stick	OD	0.78;3.5	CS+IMT(1)	189	No	0.0;0.1	239	Cataract
14	5	1215	Intraocular Surgery details NA	OD	Fixates and follows; 4.0	CS+IMT(2)	70; lost to follow-up	No	Not fixating; 4.0	76	Subretinal fibrosis
15	11	350	S/P Vitrectomy	OD	0.78;4.0	CS+IMT(1)	120	No	0.48;4.0	406	Cataract
16	17	54	Fire cracker injury	OD	2;3.5	CS+IMT(2)	309 and ongoing	Yes (1)	0.18;3.0	380	Glaucoma; Subretinal fibrosis
17	10	50	Fire cracker injury	OD	0.78;4.0	CS+IMT(1)	30 and ongoing	No	0.18;4.0	42	Nil

However significantly in six patients the onset was delayed (range, 7 months to 40 months). With late onset of disease, often there is unreliable historical information among the pediatric age group.[17] Also poor visual outcome can result from lack of awareness of the parents about this entity with late onset of disease. Hence it is important for the treating ophthalmologist to properly counsel the parents about the possibility of developing SO in the uninvolved eye in the near future.

All patients received systemic steroids as soon as the diagnosis of SO was made, and 6 patients (35%) also received intravenous methyl prednisolone at an adequate dose prior to starting oral steroids. Subsequently, 82.3% (14 of 17) received additional immunosuppression with azathioprine or methotrexate or cyclosporine in combination with steroids. In a similar study conducted by Kumar et al. only 50% patients received immunosuppressive drugs, as compared to our series.[18] In our series, azathioprine was the preferred first line drug (10 patients), failing which to control inflammation cyclosporine was used as second line IMT. Immunosuppressives were started only after obtaining clearance from the pediatrician or internist and was closely monitored by them. All the patients tolerated immunosuppressive drugs well and none developed any untoward side effects.

There has been debate regarding the only known means of prevention of sympathetic ophthalmia, i.e. removal of the injured eye (enucleation) or its content (evisceration) within a week after the traumatizing incident. In a retrospective study of 14 pediatric patients with SO conducted by Kumar et al. there were 4 enucleations and one evisceration during the follow-up period.[18] In contrast to this, in our study there were only one evisceration and one enucleation after the onset of SO. The decision regarding enucleation or evisceration needs to be made very carefully, because the vision in the exciting eye eventually may be better than the vision in the sympathetic eye in some patients. Till now no benefit of enucleation after the onset of SO has been noted in the study, and the lack of detailed data on the timing of enucleation made it difficult, if not impossible, to draw any conclusions to this end.[19]

Surprisingly, in our study three exciting eyes were found to have vision 6/12 or better at final follow-up after the onset of sympathetic

ophthalmia. The presenting visual acuity was perception of light (PL) in these exciting eyes. Of these, two patients received immunosuppressive therapy to control the ocular inflammation. If there is reasonable doubt regarding the visual potential of an injured eye, then every effort should be made to preserve it considering the pediatric age group. With aggressive immunosuppressive therapy, good vision may be retained even in an exciting eye.

Our series also showed that 70.5% of pediatric patients with SO had a good visual outcome of 6/12 or better in the sympathizing eye, this is similar to the results found by Kumar et al.[18] Though in our series the use of immunosuppressive drugs to control inflammation was about 82%, the visual outcomes were comparable. But importantly to note is that in our series more than 80% patients had a longer follow-up duration of more than 6 months, which suggests that good visual outcomes continues to be maintained with the current treatment regimen.

To conclude, the early signs and symptoms of SO must be carefully watched for, and if the disease does develop, prompt and aggressive therapy with appropriate immunosuppression can lead to favourable visual outcomes in the sympathizing eye of pediatric patients. Creating awareness among the parents by the treating ophthalmologist of the possibility of development of SO in the uninvolved eye is of utmost importance for early recognition and management.

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This Paper was judged as the **BEST PAPER** of **VITREO RETINAL DISEASES I** Session.

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Evaluation Of The Role Of Autologous Bone Marrow Mononuclear Cells In Advanced Dry AMD

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ABSTRACT

PURPOSE

To assess the role of intravitreal Bone Marrow-derived Mononuclear Stem Cells (BM-MNCs) in patients with Advanced Dry Age-related Macular Degeneration (d AMD) and quantitatively analyse it using a newer modality - advanced retinal pigment epithelium (RPE) analysis.

METHODS

This was aprospective interventional non randomized clinical trial. 25 patients with bilateral advanced dAMD were recruited for intravitreal injection of autologous BM-MNCs. The patients were evaluated at presentation and during follow-up visits on 1, 3, 6 and 9 months to look for the course of the disease, complications if any and response over the period using Fundus Auto Fluorescence (FAF), multifocal ERG (mf ERG) and advanced RPE analysis. The fellow eye was taken as control.

RESULTS

The procedure was well tolerated without any adverse effects or decrease in best corrected visual acuity in cases. A statistically

significant decrease was noted in area and greatest linear dimension (GLD) of geographic atrophy at 9 months follow up after injection from 7.6 mm^2 to 4.98 mm^2 ($P = 0.002$) and 5.39 mm to 5.17 mm ($P < 0.001$). Improvement in mf ERG was seen as a statistically significant increase in amplitude and decrease in implicit time in cone dominated ring 1 ($<2^0$).

CONCLUSIONS

Autologous BM-MNCs transplantation by intravitreal injection is a safe option in treatment of advanced dry AMD and may help preserve degenerating retina as evident on mf ERG, FAF, and advanced RPE analysis. Advanced RPE analysis is an effective tool to determine response to newer treatment modalities in dry AMD.

KEYWORDS

Advanced RPE analysis, dry Age-related Macular Degeneration, fundus autofluorescence (FAF), multifocal electroretinogram (mf ERG), Stem cells.

INTRODUCTION

Age-related Macular Degeneration (AMD) is one of the leading causes of low vision in the elderly population in developed nations[1] and it is defined as a chronic, progressive disorder characterized by changes occurring within the macula reflective of the ageing process. The classification system proposed by Age- Related Eye Disease Study is now increasingly used to classify AMD.[2] Advanced or late AMD can be either non-neovascular (dry, atrophic, or non-exudative) or neovascular (wet or exudative). Advanced non - neovascular AMD is characterized by drusen and geographic atrophy extending to the center of the macula while advanced neovascular AMD is characterized by choroidal neovascularization and its sequelae. In late stages of AMD, there is severe visual impairment.[3] The prevalence of AMD in developing countries like India is increasing, with the prevalence of late AMD being comparable to that of the western populations in the age group 60-79 years[4] and is estimated to increase by a third by 2020.

Factors that may increase the risk for occurrence of AMD includes genetic defects including SNPs (Single Nucleotide Polymorphisms) associated with various genes e.g. CFH, CFB, C2, ARMS2 etc.[5,6] age, smoking and nutritional factors. Although vitamin supplementation can slow the progression of dry AMD in advanced forms,[3] their

evaluation of efficacy against dry AMD turns out to be difficult and time-consuming. Currently, no definitive treatment is available that can reverse dry AMD. Given that diseased RPE is the major component of AMD, attempts have been made to replace the RPE at the macula, either by moving diseased macula to the periphery or by grafting new RPE under the macula. Macular translocation and RPE transplantation are complex, lengthy and expensive procedures that often require further surgeries to address complications such as unplanned retinal detachment, cataracts, and double vision. To overcome this, it will be necessary to develop new techniques to derive and expand RPE cells in vitro or to use the paracrine effect of stem cells to trigger rejuvenation.

Currently, cell-based therapy has gained a momentum in the treatment of AMD. The neuroretina is a complex structure whose health depends on blood vessels and retinal pigment epithelium (RPE), each of which is affected differently in the spectrum of retinal disease.[7] Degeneration of neural cells in the retina is a hallmark of several ocular diseases such as Retinitis Pigmentosa, where loss of photoreceptors is a primary event or dry AMD, where there is a loss of photoreceptors secondary to damage to RPE.[8,9] Therefore three distinct cell types which are conceivable targets for cell therapy in the retina are – neuroretina (photoreceptors, bipolar cells, and ganglion cells), retinal pigment epithelium and vascular endothelial cells. The therapeutic application of stem cells is based on a variety of strategies, the most well-known of which is cell replacement therapy where exvivo differentiated stem cells are delivered to the damaged tissue in order to integrate and restore function. An alternative method is via a paracrine effect, whereby the transplanted stem cells secrete trophic factors that induce the resident tissue to self-restore and proliferate.[10] In the trophic approach, the stem cells remain undifferentiated and are intended to repair the injured tissue or preserve function by altering the cellular microenvironment either by releasing cytokines or cell-to-cell interactions.[11]

Other than clinical examination with an indirect ophthalmoscope, imaging modalities like spectral domain optical coherence tomography (SD-OCT) , fundus fluorescein angiography (FFA) and fundus auto-fluorescence imaging (FAF)[12] with a confocal scanning laser ophthalmoscope are established modalities used for evaluation of patients with AMD and there is no clear consensus about the best method.[13] This study uses and describes advanced RPE analysis as a tool to monitor the response of the treatment. Using Advanced RPE analysis software

(Cirrus 6.0) the status of the RPE can be objectively and automatically examined in detail and can be followed over time.[14] The major advantage of SD-OCT imaging lies in using only one type of scan for documenting both en-face and cross-sectional images of the retina. It, therefore, provides more detailed insight in retinal alterations of geographic atrophy patients than FAF.[15] Drusen area and volume, as well as area of geographic atrophy, can be measured and analysis results are presented along with calculated values in two clearly arranged screens.[16] Similarly response to treatment can be assessed using mf ERG by observing the changes in amplitude and implicit time.[17]

In the last decade, numerous advancements have been made in the treatment of neovascular AMD with good results. However treatment of advanced forms of dry AMD i.e. geographic atrophy still remains a grey area and there is a dire need for developing an effective treatment.

METHODS

This study was approved by Institute Ethics Committee, and was carried out at our Centre in association with the dept. of Stem cell facility and Haematology. A total of 25 patients with bilateral advanced dry AMD with geographic atrophy were recruited. Written informed consent was taken from every patient and also the attendants of the patient, format of which was approved by the Institute Ethic Committee (IEC-AIIMS) and Institute Committee for Stem Cell Research and Therapy (ICSCRT). Inclusion criteria included a diagnosed case of dry advanced AMD with age ≥ 50 years, with stable or downhill clinical course over 6 months, with BCVA <6/60 (20/200), with media clarity, pupillary dilatation and patient cooperation sufficient for examination. Exclusion criteria were optic disc disease like glaucoma, optic atrophy from other causes, macular oedema, neovascular AMD, and bleeding disorders.

The eye with worse vision or more severe disease in case of similar vision in both eyes fulfilling the inclusion criteria was selected for injection of stem cells and the fellow eye was taken as control. The decision for intervention was taken by the principal investigator.

DATA COLLECTION

Visual function assessment

Best corrected visual acuity was assessed on a log MAR (logarithm of the minimum angle of resolution) scale by using backlit Early Treatment Diabetic Retinopathy Study chart.

Advanced RPE Analysis

The Advanced RPE analysis software is part of the new cirrus 6.0™ HD OCT (Carl Zeiss Meditec AG) providing two new algorithms and allows for the detection of morphologic alterations over time, which should – in conjunction with functional testing – aid in the stratification of stages of disease progression.[18] It provides simultaneous measurement of geographic atrophy along with three-dimensional visualization of the RPE and thus can comfortably be used to gain new insight into microstructural changes underlying disease progression.

Patients were dilated with 1% Tropicamide eye drops and a macular cube scan 512x128 was performed. Using automated Advanced RPE analysis software, the data was recorded with fovea well centred on imaging at the initial visit and each of the follow-up scans. An automated fovea localization algorithm assures that measurements from regions within circles of 3 and 5 mm centred on the fovea are compared, and as data of prior and current visit are placed side by side, changes between visits are easily detectable and can be followed over time. The area of sub RPE illumination denotes area of GA.

Multifocal Electroretinogram

mf ERG recording was done using Monpack3™ (Metrovision). Standard mf ERG recording in a fully dilated light adapted state was done for 5 minutes with monocular stimulation, (other eye occluded using occluder) following ISCEV guidelines, using fixation target - MERG61BF to check for fixation and done at viewing distance of 33 cm corresponding to a field of 30^{o} horizontally and 24^{o} vertically, flashed in a pseudorandom pattern on a dark background cover with a luminance of 30 cd/m^2 at a frequency of 17 Hz to optimize the amplitude of responses.[19] Serial records were analysed to check for any change in parameters.

Fundus Auto Fluorescence

The procedure was carried out using VISUPAC™ (Carl Zeiss Meditec AG). The patient was dilated using 1% Tropicamide eye drops and FAF images were recorded using a blue filter. Areas of hypo-auto fluorescence in the macular region were taken as Geographic Atrophy. The greatest dimension of this hypo auto fluorescent area was measured and noted as GLD (greatest linear dimension) at baseline, which was then followed up in each follow-up using the inbuilt software.

Bone marrow aspiration

The procedure was carried out in Haematology department using a standard protocol where the patient was placed in the lateral decubitus position, with the top leg flexed and the lower leg straight. The site was prepared, cleaned with an antiseptic (Betadine) scrub, and draped, exposing the iliac crest. The skin and the area down to the periosteum was infiltrated with a local anaesthetic (approximately 10 cc of 1% Xylocaine was used). The BM aspiration needle, with a stylet in place, was inserted, advanced by rotating clockwise and counter clockwise slowly until the cortical bone was penetrated and the marrow cavity was entered, once within the marrow cavity, the stylet was removed, and approximately 25 to 35 cc of Bone Marrow was aspirated.

Bone marrow processing

All open cell handling procedures were performed in Stem cell facility, AIIMS following Current Good Manufacturing Practice (cGMP) guidelines and standard protocol under aseptic precautions The bone marrow-derived mononuclear cells (MNC) were separated by Ficoll density separation method and the sample was then diluted 1:3 with phosphate buffer saline (PBS). Bone marrow aspirate was layered over lymphocyte separation medium or Ficoll medium (Specific gravity 1.077) in 50 ml Falcon tube and centrifuged at a speed of 1800 rpm for 30 min. After centrifugation, the interface cells forming the whitish ring (buffy layer) were aspirated in a separate tube. The rest of the product was kept aside in a sterile container. The trace of ficoll was removed by three heparinized normal saline washes. Supernatant of each wash was kept in a sterile container till final product, a cell pellet was resuspended in 1 ml syringe. The final cell concentration of 8 million mononuclear cells per 0.1 ml was achieved.

Mononuclear Cells Evaluation

The aliquot of harvested mononuclear cells was evaluated for viability (Trypan blue dye exclusion test), morphology using Giemsa stain (figure 1), cell count using Neubaur chamber and was characterized using antibodies directed against CD-34 flow cytometry (figure 2).

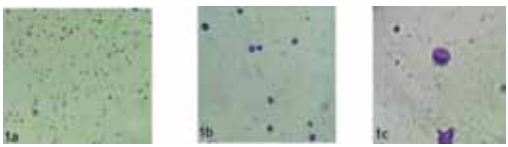

Fig. 1: Representative Light Microscope Image of Giemsa-stained MNCs (left) a. 10x magnification image (middle) b. 40x magnification image (right) c. 100x magnification image

Flow Cytometry

Around 0.5 × 106 MNCs from bone marrow were stained with CD-34 for 30 minutes at 4°C. Parallel appropriate isotope controls were also stained. All samples were rinsed twice in PBS and analysed on a FACS LSR-II (BD Biosciences) and analysed using software FACS DIVA 6.12 (BD Biosciences). At least 10,000 cells in total were analysed (Figure2).

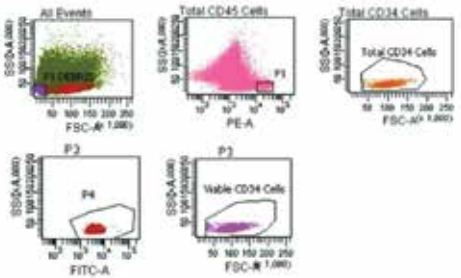

Fig. 2: Representative plot for CD34 enumeration. Quantification of MNCs by flow cytometry. Cell distribution based on FSC (forward scatters) and SSC (side scatter) parameter that describe their size and granularity

Sterility

An aliquot of bone marrow and isolated mononuclear cells was sent for microbiological culture evaluation. The results of microbial cultures were reviewed by the laboratory in charge in a timely manner.

Intravitreal Injection

BM-MNC were suspended in physiological saline to a concentration of 8 million cells in 0.1 ml and were injected into the mid-vitreous with the help of 26 G needle by the pars plana route under topical anaesthesia under aseptic precautions. Any sign of infection like endophthalmitis, intraocular pressure elevation, vitreous haemorrhage, cataract development or progression and anterior chamber reaction was noted on subsequent follow-ups.

RESULTS

The mean volume of bone marrow aspirate was 25 ±8 ml. The total cell count was 8 million per 0.1 ml normal saline with viability being 98 ±1%. No growth of microorganisms was noted in any of the cultures in our study.

Twenty five patients (15 male and 10 female) with a mean age of 64.4 years were included in the study. The eye in which intravitreal stem cell injection was given was considered as case and the fellow eye as a control. No sign of infection like endophthalmitis, intraocular pressure elevation, vitreous haemorrhage, cataract development or

progression and anterior chamber reaction was noted on subsequent follow-ups in post stem cell injection in patients.

There was no significant change in mean Best-corrected visual acuity (BCVA) from pre-injection value of 1.24±0.28(20/347.5) as compared to the post injection value of 1.11±0.41(20/257.6) at 9 months of follow-up (P = 0.07) (Paired t test). (Table 1)

Table 1 Best corrected visual acuity – case and controls

	Pre-injection	1 month	3 months	6 months	9 months	P value
Case	1.24 ±0.28	1.24 ±0.35	1.16 ±0.42	1.12 ±0.40	1.11 ±0.41	0.07
Control	1.15 ±0.39	1.16 ±0.39	1.17 ±0.37	1.21 ±0.31	1.24 ±0.36	0.23

Mean values (log MAR) ± Standard deviation

Advanced RPE analysis

There was a statistically significant decrease in the size of geographic atrophy as measured by advanced RPE analysis with pre-injection mean value of 7.6 mm^2 decreasing to 4.98 mm^2 at 9 months post procedure (P= 0.002) (Wilcoxon signed rank test). The improvement was noticed to be stable at 9 months follow-up of patients. (Table 2)

Table 2 Sub-RPE illumination – case and controls

	Pre-injection	1 month	3 months	6 months	9 months	P value
Case	7.6±4.6	6.55±4.12	5.48±3.61	5.07±3.39	4.98±3.2	0.002
Control	7.95±3.95	8.3±4.02	8.4±4.09	8.74±4.1	9.15±4.06	0.009

Mean values (mm^2) ± Standard deviation

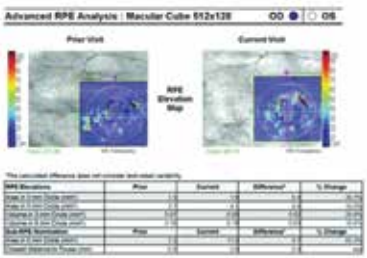

Fig. 3a: Change in Sub-RPE illumination in control on two consecutive visits

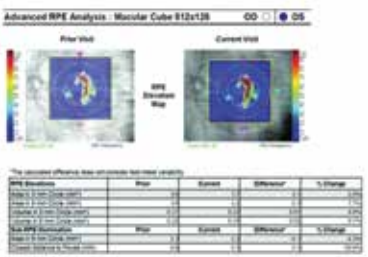

Fig. 3b: Change in Sub-RPE illumination in case on two consecutive visits

Multifocal ERG

Analysis of mf ERG in cases showed improvement at 9 months as noted by a statistically significant increase in amplitude in ring 1(<20) from a baseline value of 500.85 nV/deg 2 to 586.98 nV/deg 2 and

3(5 – 100) from a baseline value of 311.19 nV/deg 2 to 454.8 nV/deg 2 (P= 0.03 and 0.001 respectively, Wilcoxon signed rank test) and decrease in implicit time in ring 1(<20) from a baseline value of 48.06 msec to 42.7 msec and 5 (>150) from a baseline value of 48.34 msec to 43.98 msec (P= 0.013 & 0.001 respectively, Paired t test), while in control group there was decrease in mean amplitude in all the rings. (Table 3 and 4). The change in implicit time in the control group was not significant.

Table 3: mf ERG amplitude (mean values in nv/deg2) - case and controls

Ring	Group	Pre-procedure	1 month	3 months	6 months	9 months	P value
<2^0	Case	500.85	366.12	493.16	583.43	586.98	0.03
	Control	541.64	409.96	537.07	525.8	527.68	0.728
2-5^0	Case	375.18	266.66	400.17	416.18	421.66	0.82
	Control	425.91	299.04	346.3	349.44	330.1	0.008
5-10^0	Case	311.19	336	399.82	435.9	454.8	0.001
	Control	385.78	376.51	380.15	333.19	298.26	0.03
10-15^0	Case	428.23	425.08	406.78	392.86	394.18	0.96
	Control	382.95	340.14	351.4	305.79	313.99	0.20
>15^0	Case	399.81	335.06	405.66	425.39	411.78	0.09
	Control	428.01	372.43	388.88	372.38	379.03	0.33

Table 4: mf ERG implicit time (mean values in msec) - case and controls

Ring	Group	Pre-procedure	1 month	3 months	6 months	9 months	P value
<2^0	Case	48.06	53.65	41.83	42.5	42.7	0.013
	Control	49.61	51.27	43.72	42.43	43.46	0.016
2-5^0	Case	46.38	46.06	42.99	42.56	42.51	0.12
	Control	48.6	49.37	46.53	50.18	51.72	0.16
5-10^0	Case	51.85	52.62	48.05	51.25	50.74	0.56
	Control	51.66	50.77	51.13	53.14	51.27	0.69
10-15^0	Case	49.8	55.64	46.96	50.92	48.9	0.58
	Control	49.39	54.26	47.47	49	49.34	0.72
>15^0	Case	48.34	46.86	44.57	43.67	43.98	0.001
	Control	45.84	44.41	44.06	44.85	43.78	0.19

Fundus Auto Fluorescence

In the group receiving the intravitreal injection, the median GLD decreased from 5.39 mm at baseline to 5.17 mm at 9 months as measured by FAF imaging. The decrease in the size of geographic atrophy in case group was statistically significant with P <0.001 (Wilcoxon signed

rank test). In the control group, the median GLD increased from 5.06 mm at baseline to 5.35 mm at 9 months.

Table 5: change in greatest linear dimension of geographic atrophy – case and controls

	Pre injection	1 month	3 months	6 months	9 months	P value
Case	5.39	5.40	5.33	5.18	5.17	<0.001
Control	5.06	5.16	5.28	5.41	5.35	0.009
Greatest linear dimension (mm)						

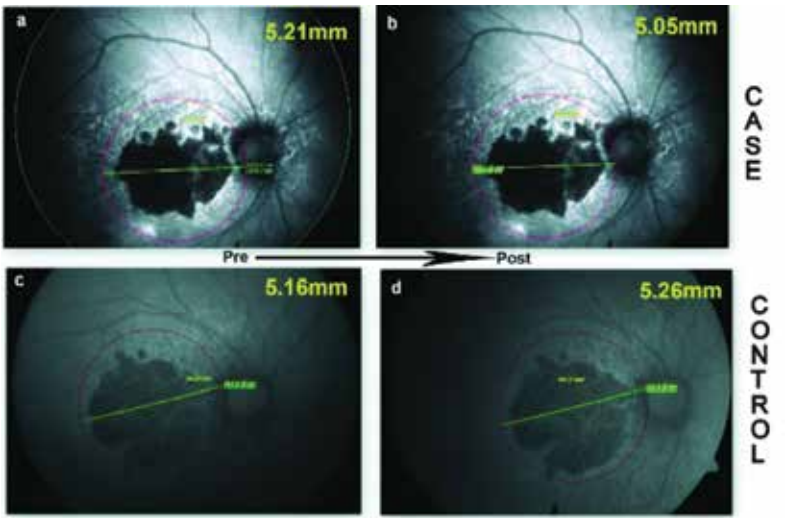

Fig. 4: Change in greatest linear dimension of geographic atrophy – case and control. (a) greatest linear dimension of a case prior to intervention. (b) greatest linear dimension of same case 6 months post intervention. (c) greatest linear dimension of a control prior to intervention. (d) greatest linear dimension of same control on 6 months follow up.

DISCUSSION

The use of autologous bone marrow derived stem cells for retinal degeneration offers neuroprotection and rescue from degeneration without immune rejection. In this study, we utilized autologous BM-MNCs in cases with advanced dry AMD and evaluated the change in above mentioned parameters at various follow-ups. We injected 8 million mononuclear cells/0.1 ml and is based on available preclinical safety data, that is, 10 million mononuclear cells per eye.[20] Both the bone marrow aspiration and intravitreal injection were well tolerated without any ocular and systemic adverse effects. Our findings were

consistent with previously done preclinical study in NOD-SCID mice showing no long term ocular or systemic safety concerns associated with intravitreally injected BM cells.[21]

Intravitreal injection of CD 34+ cells results in homing of these cells into the damaged retinal tissue. Trans retinal migration of these CD 34+ cells into the outer retina has been demonstrated by Calzi et al in an animal model of laser retinal injury.[22]

In this clinical study, histopathological analysis to confirm the intraretinal incorporation of these CD 34+ cells following intravitreal injection was not possible as was done in animal studies carried out by Otani et al.[23] The intravitreally injected bone marrow stem cells help in preserving the degenerating retina in more than one way. As shown by Otani et al stem cells cause significant up-regulation of many antiapoptotic genes, including small heat shock proteins and transcription factors in the two mouse models of retinal degeneration, rdl, and rdl0. Second, the injected stem cells may differentiate into retinal neural cells as shown by Tomita et al.[24] Intravitreal route of injection is a safe procedure and its clinical feasibility has been shown in previous studies done by Jonas et al, Park et al and Kumar A et al.[25,26,27]

In our study we used intravitreal injection of autologous bone marrow derived mononuclear stem cells, while in an another study done in Asian population by Song WK et al[28] using sub retinal injection of embryonic stem cells in dry AMD showed similar improvement in vision in treated eye, with deterioration in the control group. However, a longer duration of study is required to assess the effect on visual acuity. Advanced RPE analysis of post stem cell injection in dry AMD patients showed decrease in the area of geographic atrophy at 9 months follow-up period in the intervention group, along with a decrease in greatest linear dimension of geographic atrophy (mm) measured by FAF and improvement in implicit time in ring 5 in mf ERG. The effect of stem cells on geographic atrophy size can be explained by homing of stem cells to the injured retinal sites and stabilization of retinal vasculature and RPE by trophic effects, preventing further increase in the area of atrophy. The predominantly rescued cells in Stem cells injected eyes were the cone photoreceptors in the mouse model of rd1 and rd10 in Otani and colleagues study. There is an improvement noted in mfERG in cases, which is a cone-derived

response and correlates well with histopathological examination of mice retinas in Otani experiment.

With the new Advanced RPE analysis software that allows automated, quantitative assessment of atrophic lesions along with temporal monitoring of disease progression, the efficacy of various modalities used in future similar clinical trials could be assessed quantitatively using the tool.

However, the long-term efficacy and dose standardization of autologous bone marrow derived mononuclear stem cell injections is still to be determined.

In conclusion this study shows that autologous bone marrow-derived mononuclear stem cells transplantation by intravitreal injection is a safe procedure and promising therapy in retinal degenerations like dry AMD as evident by the decrease in GA over time and a significant improvement on advanced RPE analysis and mf ERG. Advanced RPE analysis is an effective tool to determine the stage, prognosis as well as response to various newer treatment modalities in dry AMD.

DISCLOSURES

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Conflict of interest

None of the authors has conflict of interest with this submission.

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Comparison Of Standard And 'Innovative Wide-Field' Optical Coherence Tomography Images In Assessment Of Vitreo-Retinal Interface In Proliferative Diabetic Retinopathy

Dr. Mishra Divyansh Kailash Chandra, Dr. Mahesh Shanmugam P, Dr. Rajesh Ramanjulu, Dr. Vinaya Kumar Konana

INTRODUCTION

Since its invention, optical coherence tomography (OCT) has made remarkable advancements in both image resolution and acquisition speed. Recent improvements to commercially available OCT systems have also included increasing scan length.The new DRI OCT Triton plus (Topcon, Tokyo, Japan), a commercially available, swept-source OCT system, is capable of producing a 12 mm scan. A novel yet simple technique to expand the scan length on OCT has been reported as an extended field imaging (EFI) technique which involves imaging the posterior pole through trial frames fitted with a +20 diopter lens.[1] Wide-field OCT imaging is advantageous over conventional OCT imaging because a more comprehensive assessment of the posterior pole can be made with a single scan. It also has the ability to detect abnormalities of the vitreomacular interface in great detail. Preoperative OCT assessment of associated vitreomacular interface abnormalities in patients with diabetic retinopathy requiring vitrectomy can assist in decision making preoperatively in terms of accurate plane of dissection as they would have, an incomplete posterior vitreous detachment with multiple focal attachments. In this study, we sought to further explore the feasibility of EFI technique in aiding us doing diabetic vitrectomy with minimal complications.

METHODOLOGY

This study was a prospective study of thirty eyes from 22 patients with proliferative diabetic retinopathy who visited Sankara Eye Hospital between January 2017 and May 2017. This study was approved

by the Institutional Review Board was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki.The eyes with poor quality images due to media opacities or poor fixation wereexcluded from the study.

A set of 12 mm radial scans centered on fovea and another set centered on optic disc were captured in all subjects with standard technique and with a novel EFI OCT technique. OCT images were captured with DRI OCT triton plus. The EFI technique involved imaging the posterior pole through trial frame fitted with a +20.00 diopter lens (planoconvex) with convex surface facing the eye, then the expansion rates were calculated using ImageJ software (NIH) (http://imagej.nih.gov/ij/).

We analyzed the image quality by assessing the visibility of ellipsoid zone in normal area of retina and the lateral edges of OCT scan. The image quality was graded with a scale of 1 to 3 with 1 being the poor quality and 3 being the best. Reflection artifacts and rim artifacts were analyzed. The vitreoretinal interface was analyzed based on the visibility of posterior and anterior attachments. Superotemporal and inferotemporal attachments were assessed in fovea centered scan. Superonasal and inferonasal attachments were assessed in disc centered scan. The above parameters were compared between standard and EFI images.

RESULTS

A total of 30 eyes of 22 patients were included in the study of which were 12 were male and 10 were female. The mean age group was 51 years. A total of 10 patients had vitreomacular traction, 5 patients had taut posterior hyaloids, 8 patients had traction retinal detachment involving macula and 7 patients had traction involving disc and papillo macular bundle. The scan length was increased by a factor of 1.55 when obtained using EFI technique. Of the 30 disc centered scans 6 scans were not centered in standard OCT and 13 scans were not centered in EFI OCT. In the 30 fovea centered scans 7 scans were not centered in standard OCT and 12 scans were not centered in EFI OCT. In standard OCT images 86.6% were of grade 3 whereas in EFI 58% were of grade 3. No artifacts were seen in standard OCT. Reflection artifacts were absent in standard OCT but 36% of eyes showed reflection artifacts in EFI images. Rim artifacts were absent in standard OCT but 22% of eyes had rim artifacts in EFI images.

Out of 30 eyes, vitreoretinal separation was noted in 21 eyes in superotemporal and inferotemporal quadrant of which anterior extent of attachments were made out in 15 eyes using EFI technique where

as in only 08 eyes it could be made out in standard OCT. In twelve eyes, vitreoretinal separation was seen in superonasal and inferonasal quadrant, of which in 9 eyes anterior extent was noted in EFI technique and in 5 eyes it was noted using standard techniques.

DISCUSSION

A convex lens placed between the eye and the OCT machine theoretically increases the imaging light incidence angle resulting in imaging field expansion. The convex lens causes least angular minification of the target which also increases the field of OCT. Since the eye is a globular structure, the concavity of posterior pole also contributes to increase in the scan length. The field of expansion in EFI technique is increased by a factor of 1.5. Furthermore, EFI results in a decrease in image resolution because EFI does not change the hardware capabilities of the OCT system. It simply magnifies each pixel, so the detailed information is missed, but there is no gross loss of details of the retinal architecture. Reflection and rim artifacts are common with the EFI technique. Reflection artifacts though present did not hamper visualization of details in majority of cases. Assessment of vitreoretinal interface plays an important role in diabetic vitrectomy. Identification of surgical plane is of utmost importance to proceed with a successful surgery.[2,3] The EFI technique enables us to identify the anterior extent of attachment thus aiding us in plane of dissection. The colour photo of fundus cannot be seen in detail because of reflection of light produced by the lens but can be compensated by looking into the projection image. The EFI technique has also been employed to OCT Angiography to evaluate the non perfusion areas in retinal vein occlusion.[4] Further EFI OCT can also be tried in acquiring images for mid peripheral lesions. The limitations of our present study include the fact that this was a study that only included a limited number of patients. In summary, EFI technique can be used effectively in assessing the vitreoretinal interface abnormalities in diabetic retinopathy and also aiding us in identification of correct cleavage plane in diabetic vitrectomy. The technique is effective, economical, simple to implement, easy to perform, and uses readily available materials.

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Morphometric Analysis Of Treatment Resistant Pigment Epithelial Detachment After Intravitreal Ziv-Aflibercept In Chorioretinal Disorders

Dr. Jay Sheth, Dr. Giridhar Anantharaman, Dr. Mahesh G, Dr. Shruti Chandra

ABSTRACT

PURPOSE

Intravitreal ziv-aflibercept (IVZ) is emerging as a low-cost alternative for management of macular disorders in developing countries. The purpose of our study was to evaluate the short-term safety and efficacy, including morphological response of IVZ based on spectral domain optical coherence tomography (SD-OCT) in diversechorioretinal disorders.

METHODS

Prospectively, 10 eyes with varied pathologies such as PCV (3 eyes), Wet AMD (3 eyes), chronic CSCR (2 eyes) and neovasculopathy (PCN; 2 eyes) underwent IVZ therapy. At baseline, all patients underwent multimodal imaging including SD-OCT, ICGA, DFA and FAF (Spectralis) while SD-OCT was repeated at 1 month. Changes in BCVA, intraretinal fluid (IRF), subretinal fluid (SRF), subfovealchoroidal thickness (SFCT), along with dimensions (height, base diameter, area) of PED at maximum extent & shallow irregular PED (Double layer sign; DLS) were analysed at baseline and at 1 month. Detailed analysis of outer retinal layers (Ellipsoid zone, ELM, Hyperreflective dots), DRIL and VMIA was performed too.

RESULTS

Compared with baseline, significant reduction was seen in height, base diameter and area of PED respectively (p=0.02, p=0.01, p=0.02) at 1 month. Statistically significant reduction was also noted in SFCT (p=0.0009), DLS height (p=0.01) and SRF height (p=0.01). 40% and 37.5% of eyes had complete resolution of IRF and SRF respectively. Improvement was noted in BCVA, DLS width and CMT, although not significantly. On detailed analysis, one eye showed complete resolution of DLS. At baseline, RPE rip was present in 7 eyes which showed early resolution in 2 eyes. Similarly, ELM disruption showed improvement in 4 out of the 9 eyes while ellipsoid disruption did not show any sign of restoration at one month in all 10 eyes. Likewise, disorganization of inner retinal layers (DRIL) improved in 1 out of the 5 eyes while reduction in hyperreflective dots was seen in 7 out of the 10 eyes. One eye has ERM which remained unchanged. None of the patients experienced any serious ocular or systemic adverse events.

CONCLUSION

Single intravitreal injection of ziv-aflibercept has promising anatomical outcomes on PED, besides achieving a dry macula, maintaining stable visual acuity with an acceptable safety profile. Morphometric improvement in choroidal thickness and integrity of disorganized retinal layers along with its low-cost favours its use as an efficacious anti-VEGF agent in the developing world.

INTRODUCTION

Anti-vascular endothelial growth factor (Anti-VEGF) therapy have become the treatment of choice for choroidal neovascularization secondary to wet age related macular degeneration (ARMD) and pachychoroid disorders.[1,2] Currently, the US-FDA (Food and Drug Administration) has approved pegaptanib (Macugen; Eyetech, New York, NY), ranibizumab (Lucentis; Genentech, S. San Francisco, CA/ Roche, Basel, Switzerland), and aflibercept (Eylea; Regeneron, Tarrytown, NY) for intraocular use.[3-5] However, in the American society of Retina Specialists (ASRS) Preferences and Trends Survey conducted in 2015, which was on basis of the current body of literature and considering the cost-effectiveness of bevacizumab (Off-label use; AVASTIN, Genentech, Inc.), 64% of the US retinal physicians used bevacizumab as the first line treatment for AMD and and > 80% of US members

treated choroidal neovascularization from histoplasmosis and other non-AMD causes with bevacizumab.[6]

Amongst the anti-VEGF agents, aflibercept is emerging as an effective alternative, especially for non-responders. However, the cost of aflibercept ($ 1,850/ dose) is major hindrance for its widespread use, especially in developing nations. Ziv-aflibercept (Zaltrap; Regeneron) is a recombinant fusion protein of 115 kDA, composed of the extracellular VEGF binding domains from human VEGF receptors 1 and 2 fused to the Fc portion of a human IgG1.[7] It is approved by the FDA for management of metastatic colorectal carcinoma.[7] Its off-label intravitreal use has been documented to be safe and effective for management of chorioretinal pathologies such as wet AMD, polypoidal choroidal vasculopathy (PCV), diabetic macular edema (DME) and so on.8, 9 However, a detailed evaluation of multimodal imaging features secondary to IVZ remains unexplored.

The purpose of our study was to perform a comprehensive morphometric analysis of efficacy of IVZ in variety of chorioretinal disorders. Additionally, we also evaluated the ocular and systemic safety profile of IVZ therapy.

METHODS

It was a prospective study of 10 eyes of 9 patients with varied chorioretinal disorders presenting to the Vitreo Retina Clinic of Giridhar Eye Institute, India, between January 2017 and February 2017. The study was conducted in accordance to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board. Written informed consent was obtained from each patient.

The etiologies included polypoidal choroidal vasculopathy (PCV; 3 eyes), wet age related macular degeneration (Wet AMD; 3 eyes), chronic central serous chorioretinopathy (CCSCR; 2 eyes) and pachychoroid neovasculopathy (PCN; 2 eyes).

At baseline and at one month, all patients underwent detailed clinical evaluation including assessment of best corrected visual acuity (BCVA) on Snellen chart, intraocular pressure (IOP) measurement by Goldmann applanation tonometry (AT), along with anterior segment and fundus evaluation by slitlamp biomicroscopy and indirect ophthalmoscopy. Multimodal imaging was performed including spectral domain optical coherence tomography (SD-OCT); Central macular thickness [EDI-OCT], fundus autofluorescence (FAF), digital fluorescein angiography

(DFA), and ICGA (Spectralis HRA + OCT, Heidelberg Engineering, Heidelberg, Germany) while SD-OCT was repeated at 1 month.

Image Analysis

Subfoveal choroidal thickness (SFCT) was measured manually with the help of built-in calipers in OCT software (Figure 1). Measurements were taken from the outer portion of hyperreflective line corresponding to the RPE to the inner portion of hyperreflective zone corresponding to the choroidoscleral junction by a single masked observer (J.S.). They were obtained in the subfoveal region (subfoveal choroidal thickness; SFCT). Automated central macular thickness (CMT) was also calculated using the 25 line raster scan protocol.

A dense scan was carefully analysed to look for maximum extent of PED and Double layer sign (DLS; defined as two hyperreflective layers separated by a gap - the inner layer is the hyperreflective irregularly elevated RPE and the outer layer is the inner layer of the Bruch's membrane) and subsequently, their dimensions including the height, width and area were calculated using the built-in calipers (Figure 1B and 1C). PED was evaluated for presence or absence of any notch, type of reflectivity (Hyper, hypo, mixed) and for underlying pachyvessel. Presence of pachyvessel was also evaluated underlying the DLS along with the reflectivity of DLS (Hyper, hypo, mixed). In cases where pachyvessel was present in associated with either PED or DLS, the choroidal thickness was also measured in that location (Figure 1C).

The sections were also evaluated for presence or absence of intraretinal fluid (IRF) and subretinal fluid (SRF). In eyes with presence of SRF, the maximum vertical extent was measured manually (Figure 1A). Additionally, in the section with maximum extent of PED, a detailed analysis was performed of the outer retinal layers. This included scrutinizing the integrity of the retinal pigment epithelium (RPE) (Figure 1D), ellipsoid layer (EZ) and external limiting membrane (ELM), and looking for presence of intraretinal hyperreflective dots, disorganization of outer retinal layers (DRIL) and vitreomacular interface abnormalities (VMIA). DRIL was considered to be present when it affected more than 50% of central 1mm zone. VMIA included epiretinal membranes (ERM) and vitreomacular traction (VMT).

Baseline ICGA was analysed for features such as dilated choroidal vessels, nodular hypercyanescence, abnormal vascular network, blocked cyanescence and mid-phase hypercyanescence. Furthermore,

DFA was examined for various types of hyperfluorescence and hypofluorescence along with features of occult and classic CNVM

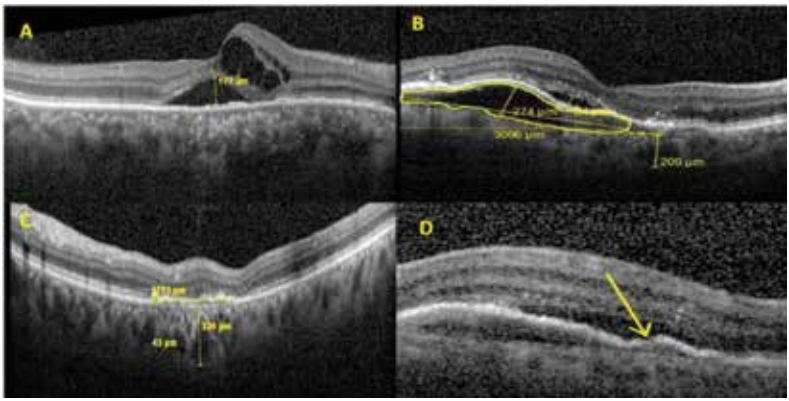

Fig. 1: Baseline spectral domain optical coherence tomography (SDOCT) measurements - A) Measurement of subretinal fluid (SFR); B) SDOCT of a patient illustrating measurement of subtrentinal fluid, pigment epithelial detachemtn (PED) parameters - height, base diameter, and area and choroidal thickness; C) SDOCT demonstrating measurement of height and base diameter of the double-layer sign (DLS) and choroidal thickness; D) SDOCT of a patient at baseline demonstrating retinal pigment epithelial (RPE) rip (Yellow arrow).

Intravitreal Injection

Ziv-aflibercept is available in vials of 100 mg / 4 ml (1.25 mg / 0.05 ml). Injection ziv-aflibercept is stored under recommended conditions and details are checked prior to aliquoting. Aliquoting is performed by a vitreo-retinal fellow under all aseptic precautions using a single 26-G needle prick technique, whereby only the syringes are changed leaving the needle in its place. 0.05 ml of ziv-aflibercept is aliquoted in tuberculin syringe, placed in a sterile cloth and then stored in a sterile tray which is kept in a refrigerator under 2^{o} C -8^{o} C.

All intravitreal injections are performed in an OT complex. With the patient in supine position, the eye is confirmed by fundus examination followed by administered subconjunctival anesthesia (0.5 mL of 2% lignocaine) in inferotemporal quadrant. 5% povidine iodine is instilled allowing a five-minute contact period. Subsequently, 0.05 ml of IVZ is given in the inferotemporal quadrant 3.5 mm away from the limbus with a 30-gauge needle under all aseptic precautions. The eye was then patched after instilling 5% povidine iodine drops and moxifloxacin

ointment for 4 hours. After the injection, topical moxifloxacin is prescribed for a period of 14 days.

Changes in BCVA, IRF, SRF, SFCT, dimensions of PED and DLS were analysed at baseline & at 1 month. Alternation in integrity of outer retinal layers (RPE, EZ, ELM), DRIL and VMIA was also evaluated at end of 1 month. Statistical analysis was done using the SPSS software, version 16.0 and statistical significance was set at p value of 0.05.

RESULTS

The mean age of the study population was 69 ±12.04 years of which 77.78% (7 patients) were men and 22.22% (2 patients) were women.

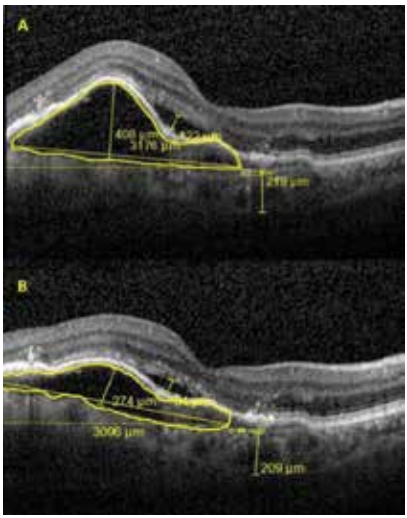

Fig. 2: Spectral domain optical coherence tomography (SDOCT) of a parient illustrating significant reduction in choroidal thickness, subretinal fluid and pigment epithelial detachment (PED) parameters - height, base diameter, and area at one month post intravitreal ziv-aflibercept (IVZ) (B) ass compared to baseline (A).

Compared with baseline, statistically significant reduction was noted in height, base diameter and area of PED respectively (p=0.02, p=0.01, p=0.02) at one month (Table 1) (Figure 2A). Five eyes each showed presence of notched PED and associated pachyvessel with PED. There was no significant difference in CT at level of pachyvessel at end of one month (p = 0.07) (Table 1). Six eyes had mixed PED reflectivity while hyperreflectivity and hyporeflectivity was present in two eyes each. In one eye, the PED reflectivity changed from hyper to mixed type post IVZ with early RPE regeneration.

DLS was present in 8 eyes with hyporeflectivity seen more frequently (6/8 eyes) than hyperreflectivity (2/8 eyes). All 8 eyes had pachyvessel associated with the DLS. No significant change in CT was noticed at level of pachyvessel (p = 0.08) (Table 1). Statistically significant

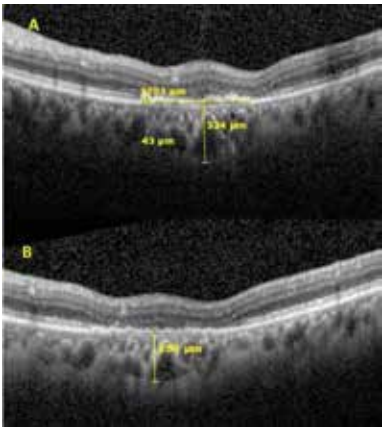

Fig. 3: Spectral domain optical coherence tomography (SDOCT) of a patient illustrating significant reduction in choroidal thickness and complete resolution of the double-layer sign (DLS) at ine month post intravitreal ziv-aflibercept (IVZ) (B) as compared to baseline (A)

reduction was noted in the height of the DLS (p = 0.01) whereas the width did not change significantly (p = 0.12) (Table 1). One eye demonstrated complete resolution of the DLS (Figure 3).

Complete resolution of IRF and SRF was seen in 40% and 37.5% of eyes respectively. SRF height also showed significant reduction (p = 0.01) (Table 1). SFCT was significantly reduced at the end of one month (p=0.0009) (Table 1) (Figure 4A and B). The eyes also showed an improvement in BCVA and CMT, although it was not statistically significant (Table 1).

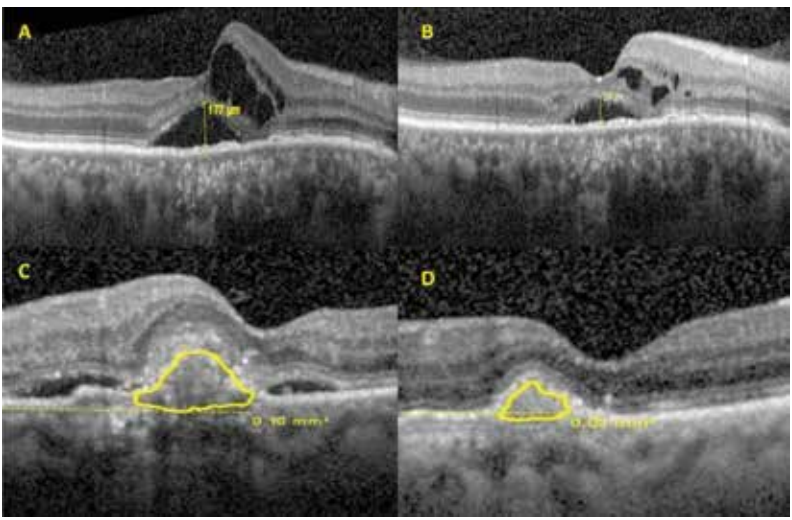

Fig. 4: Spectral domain optical coherence tomography (SDOCT) of a patient illustrating significant reduction in subretinal fluid (SRF) and intraretinal fluid (IRF) at one month post intravitreal ziv-aflibercept (IVZ) (B) as compared to baseline (A). Similarly SDOCT of another patient demonstrating significant reduction in pigment epithelial detachment (PED) are with complete resolution of SRF at one month post intravitreal ziv-aflibercept (IVZ) (D) as compared to baseline (C).

Table 1: Changes in BCVA and SD-OCT parameters at baseline and one month post intravitreal ziv-aflibercept			
Parameter	Baseline	1 Month post-IVZ	p-value
BCVA	0.48 ± 0.297	0.46 ± 0.327	0.73
SFCT	215.7 ± 130.09 µm	201.6 ± 129.93 µm	0.009
CMT	365.2 ± 103.9 µm	317.7 ± 87.24 µm	0.11
PED Base Diameter	1884.9 ± 1433.02 µm	1753.7 ± 1431.08 µm	0.02
PED Height	344.8 ± 274.95 µm	272 ± 217.88 µm	0.01
PED Area	0.57 ± 0.63 mm^2	0.44 ± 0.49 mm^2	0.02
CT at pachyvessel associated with PED	132.9 ± 168.53 µm	118.8 ± 148.97 µm	0.07
DLS Height	35.5 ± 20.88 µm	23.40 ± 22.54 µm	0.01
DLS Width	996 ± 716.05 µm	702 ± 773.92 µm	0.12
Choroidal Thickness at DLS	226.5 ± 145.07 µm	203 ± 134 µm	0.08
SRF Height	104.2 ± 67.53	41.9 ± 49.1	0.01

IVZ: Intravitreal ziv-aflibercept; BCVA: Best corrected visual acuity; SFCT: Subfoveal choroidal thickness; CMT: Central macular thickness; PED: Pigment epithelial detachment; CT: Choroidal thickness; DLS: Double layer sign; SRF: Subretinal fluid

On detailed analysis, at baseline, RPE rip was present in 7 eyes which showed early resolution in 2 eyes (Table 2) (Figure 5). Similarly, ELM disruption showed improvement in 4 out of the 9 eyes (Figure 6) while ellipsoid disruption did not show any signs of restoration at one month in all 10 eyes (Table 2). Likewise, DRIL improved in 1 out of the 5 eyes (Figure 6) while reduction in hyperreflective dots was seen in 7 out of the 10 eyes (Table 2). One eye has ERM which remained unchanged (Table 2). None of the patients experienced any serious ocular or systemic adverse events.

Table 2: Changes in micromorphic parameters on SD-OCT at baseline and one month post intravitreal ziv-aflibercept		
Parameter	Baseline (number of eyes)	Resolution one month post-IVZ (number of eyes)
RPE Rip	7	2
EZ Disruption	10	0
ELM Disruption	9	4
DRIL	5	1
Hyper reflective IR dots	10	7 (reduced)
VMIA	1 (ERM)	0

IVZ: Intravitreal ziv-aflibercept; RPE: Retinal pigment epithelium; EZ: Ellipsoid disruption; ELM: External limiting membrane; DRIL:

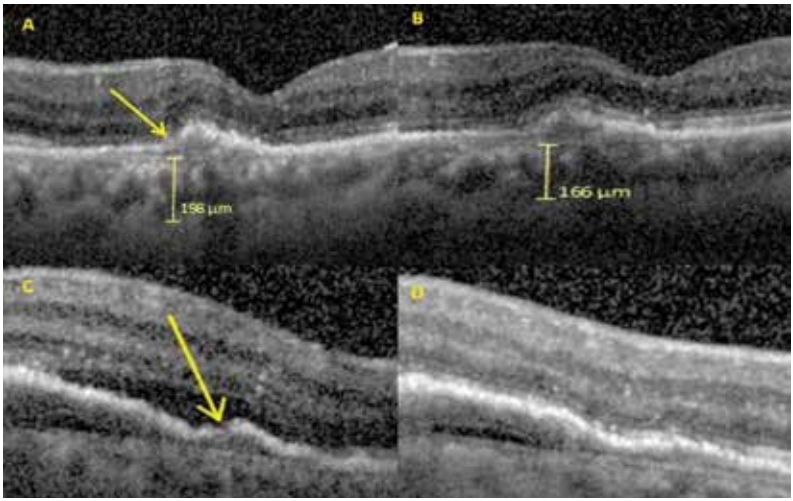

Fig. 5: Spectral domain optical coherence tomography (SDOCT) of a patient showing presence of retinal pigment epithelial (RPE) rip (Yellow arrow) at baseline (A) which showed signs of early resolution at one month post intravitreal ziv-aflibercept (IVZ) along with reduction in choroidal thickness (B); Similarly, SDOCT of another patient also similarly demonstrating resolution of RPE rip at one month (D) when compared with baseline (C; Yellow arrow).

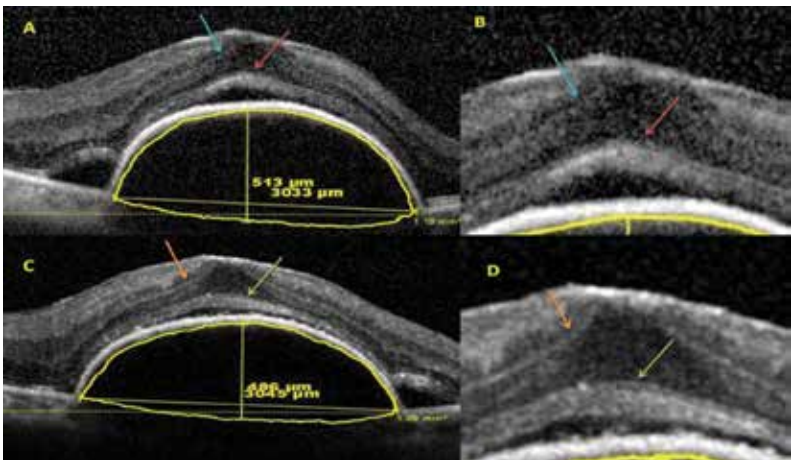

Fig. 6: Spectral domain optical coherence tomography (SDOCT) of a patient at baseline (A: Normal, B: Magnified image) and at one month post intravitreal ziv-aflibercept (IVZ) (C: Normal, D: Magnified image). At baseline, there was presence of significant disorganization of outer retinal layers (DRIL); Blue arrow in A and B and disruption of external limiting membrane (ELM: Red arrow in A and B). At one month, there was significant improvement in DRIL (Orange arrow in C and D) and restoration of ELM (Green arrow in C and D). Additionally, the pigment epithelial detachment (PED) parameters - height, base diameter, and area also show significant reduction at one month (C) as compared to baseline (A).

Disorganization of outer retinal layers; IR: Intraretinal; VMIA: Vitreomacular interface abnormalities; ERM: Epiretinal membrane

DISCUSSION

In the past decade, anti-VEGF agents have become the standard of care for various chorio-retinal disorders. Amongst the various choices available, aflibercept is considered the first line agent based on results of multiple landmark trials.[5,10,11] Nonetheless, the cost of aflibercept remains a major deterrent to its widespread use in developing nations. Ziv-aflibercept is a biosimilar to aflibercept, but has a different buffer solution and undergoes a different purification process.[12] Being an economical option, over the past few years, ziv-aflibercept has been successfully used for management of various chorioretinal disorders such as wet AMD, PCV, and DME and so on.[8,9,13,14] However, its use in PCN and chronic CSCR has not yet been described in literature. PCN is a recently described disease entity belonging to the pachychoroid disease spectrum. Its management is still evolving, but being primarily a choroidal neovascularization disease, the management involves administration of intravitreal anti-VEGF therapy.[15] In our series, we describe the use of IVZ in PCN and CCSCR for the first time in literature.

To begin with, there were few concerns regarding the use of ziv-aflibercept due to osmolarity issues. Studies evaluating the safety profile of intravitreal injections have demonstrated that osmolarity of <500 mOsm does not have any adverse effect on the RPE.[16] So, although ziv-aflibercept has an osmolarity of 1045 mOsm, its effective intravitreal osmolarity is only 312 mOsm since it is injected in about 4ml of vitreous cavity. Also, animal studies on ziv-aflibercept did not reveal any significant increase in its plasma levels after intravitreal administration.[17] Hence, ziv-aflibercept can be considered to be safe for intravitreal therapy, which has been corroborated by various studies. In the current series, we did not find any serious systemic adverse event.

In a retrospective review of 16 eyes of patients with non-responsive AMD switched to IVZ, Braimah et al did not find any significant improvement in BCVA, CMT, PED height and presence of IRF and SRF between baseline and 12 months.[18] In contrast, in our study, we found significant improvement in morphometric parameters in relation to the PED, including reduction in height, base diameter and area. Improvement in PED height and volume has been demonstrated after intravitreal aflibercept treatment by Chan et al at end of 6 months.[19]

Even de Massougnes S et al have shown improvement in PED height after aflibercept therapy at end of 1 year.[20] Improvement in PED parameters as demonstrated in our study has been seen after aflibercept use, but not yet been described after IVZ therapy in literature. Additionally, in the current study, even the DLS, which in itself is a shallow irregular PED, showed significant reduction in height, although not in the base diameter. One eye even exhibited complete resolution of DLS within one month of IVZ. Changes in DLS after IV anti-VEGF therapy has not yet been studied. Improvement in the PED parameters is a crucial outcome after single dose of IVZ since it is one of the most resistant parameter to anti-VEGF therapy and an important cause of persistent disease activity or frequent recurrences.

Mansoor et al reported significant improvement in BCVA and CMT at 1 month and 3 months post IVZ for wet AMD.[21] In contrast, Braimah et al did not find any significant improvement in BCVA and CMT at end of 12 months for refractory AMD.[18] Similarly, in our series, although we noted improvement in BCVA and CMT, it was not significant. Nonetheless, we noted significant reduction in SRF height and SFCT. 40% and 37.5% of eyes had complete resolution of IRF and SRF respectively. Reduction in choroidal thickness is a vital finding of our study since 7 of the 10 eyes belonged to the pachychoroid disease spectrum (PCV : 3 eyes, chronic CSCR : 2 eyes and PCN : 2 eyes). Although this pilot study evaluates only one month outcomes, the results are very encouraging to warrant the use of IVZ in this emerging group of disease entity, namely pachychoroid disorder.

In this study, we performed a comprehensive evaluation of individual retinal layers. RPE rip was seen in 7 eyes at baseline which showed signs of early resolution in 2 of them at the end of one month. Similarly, ELM disruption showed improvement in 4 out of the 9 eyes while ellipsoid disruption did not show any signs of restoration at one month in all 10 eyes. Likewise, DRIL improved in 1 out of the 5 eyes while reduction in hyperreflective dots was seen in 7 out of the 10 eyes. One eye has ERM which remained unchanged. These micromorphic changes are very critical in visual prognosis. Although we did not find any notable change in BCVA, the results are too short term to assess the visual outcomes effects secondary to restoration of these retinal layers. Nonetheless, the beneficial effect of IVZ on retinal layers can be postulated to have favourable long-term outcomes.

The strength of our study includes evaluation of an emerging cost-effective anti-VEGF agent, namely, intravitreal ziv-aflibercept, in wet

AMD and pachychoroid disease spectrum. We also evaluated the hitherto unstudied effect of IVZ on CCSCR and PCN. Moreover, it is a singular study to perform a detailed qualitative and quantitative assessment of IVZ on various morphological features on multimodal imaging, whereby we illustrate promising anatomical outcomes.

The limitations of our current study include the limited sample size, inclusion of patients with multiple aetiologies and short-term study. Additionally, we could not perform subgroup analysis of effect of IVZ on individual disease entity due to small sample size. However, the favourable short-term morphometric and safety outcomes is indicative of similar potentially encouraging outcomes with long-term studies and larger sample size.

In conclusion, our study demonstrates that off-label use of single dose of intravitreal ziv-aflibercept has promising retinal and choroidal morphological outcomes on multimodal imaging, besides maintaining stable visual acuity with an acceptable safety profile. Additionally, its low-cost favours its use as an efficacious anti-VEGF agent in the developing world.

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This Paper was judged as the **BEST PAPER** of **VITREO RETINAL DISEASES IV** Session.

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Optical Coherence Tomography Angiography Of The Macula After Repair Of Rhegmatogenous Retinal Detachments

Dr. Aniruddha Agarwal, Dr. Ramandeep Singh, Dr. Mangat R. Dogra, Dr. Vishali Gupta

ABSTRACT

PURPOSE

Patients with macula-off rhegmatogenous retinal detachments (RRD) may have suboptimal visual recovery despite successful reattachment due to various reasons such as loss of photoreceptors. This study was performed to evaluate the retinal microvasculature in subjects undergoing surgery for RRD using optical coherence tomography angiography (OCTA).

METHODS

In a case control study, analysis of OCTA findings of 18 eyes of 18 patients (12 males) who underwent RRD surgery at a tertiary institute were compared with 20 eyes of 20 age and gender matched healthy subjects with no known ocular disease. 3×3 mm OCTA scans were obtained in addition to enhanced depth imaging OCT. The findings on OCTA were compared with normal controls for perfusion indices and additional findings.

RESULTS

Mean age of the patients was 30.1 years and controls was 28.5 years. Six eyes had inferior RD. Seventeen eyes underwent primary scleral buckling and 1 eye underwent vitrectomy-buckle with C_3F_8 tamponade. None of the eyes had re-detachment during the follow-up at 3 months. The best-corrected visual acuity improved from counting fingers to mean of 0.73 ± 0.34 LogMAR. OCTA was performed after 3 months of surgery. Patients with RRD showed evidence of increased intercapillary spacing on *en face* OCTA. Mean vessel flow density (VFD) among patients was 34.37±0.7% and 35.27±0.2% in the superficial and deep retinal plexus, respectively, compared to 56.12 ± 2.2% and 59.64±1.9% among controls ($p<0.001$).

CONCLUSIONS

OCTA demonstrates significant reduction in mean VFD in patients after surgery for RRD. Decreased VFD may be responsible for suboptimal visual gain in these subjects after retinal reattachment.

KEYWORDS

Retinal detachment; Rhegmatogenous; Pars plana vitrectomy; Scleral buckle; Optical coherence tomography angiography; Retinal layers

INTRODUCTION

Rhegmatogenous retinal detachment (RRD) is an important cause of vision loss requiring early surgical management. The management options for RRD include surgical techniques such as scleral buckling (SB) (external tamponade) and pars plana vitrectomy (PPV) with internal tamponade (either gas or silicone oil).[1-5] Conventionally, the visual prognosis following surgery for RRD is good if the macula is attached preoperatively.[6] However, macular detachment preoperatively in cases with subtotal/total RRD results in guarded visual prognosis. In order to investigate the etiologies of suboptimal visual recovery following successful retinal reattachment, various studies have been published in the literature.[7,8] Using a number of advanced techniques such as optical coherence tomography (OCT), adaptive optics (AO) imaging,[9,10] microperimetry[11] and histopathology, correlation of visual acuity with the recovery of photoreceptors and central retinal microanatomy has been evaluated following repair of RRD.

OCT angiography (OCTA) has revolutionized the field of retinal imaging and analyses of pathophysiology of various vitreoretinal diseases such as diabetic retinopathy, age-related macular degeneration,

glaucoma, and other conditions such as uveitis and macular telangiectasia.[12] With the help of OCTA, entities such as pachychoroid spectrum disorders have been better studied. With the help of OCTA, it is possible to obtain a detailed depth-resolved reconstruction of the retinochoroidal microvasculature by utilizing endoluminal flow as intrinsic contrast. This property of the OCTA enables improved understanding of the various mechanisms that may be responsible for vision loss in vitreoretinal diseases.

In the index study, we aimed to analyze the retinochoroidal vascular factors involved in the visual recovery following successful retinal reattachment in patients with RRD using OCTA. In addition, the features on OCTA among patients with RRD were compared to normal control subjects in order to understand the pathological mechanisms behind suboptimal visual recovery.

MATERIALS AND METHODS

In the index study, patients with RRD undergoing successful retinal reattachment surgery at the Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India were included. The study was approved by the PGIMER Institutional Ethics Committee (IEC). Written informed consent was obtained from all individual participants included in the study. Those patients with anatomically reattached retina undergoing OCTA scans were included. The study adhered to the tenets of the Declaration of Helsinki and the rules laid down by Health Insurance Portability and Accountability Act (HIPAA) of 1996.

Study Subjects

Subjects undergoing retinal reattachment surgery between July 2015 to December 2016 were included in the study. The criteria for inclusion were presence of successful retinal reattachment after single surgical intervention (either primary scleral buckle or primary pars plana vitrectomy with gas tamponade), clear ocular media, and absence of macular pathologies such as scars, subfoveal fibrous bands, epiretinal membranes, or residual traction bands. The imaging with OCTA was performed after surgery for all the patients (within 1 year postoperative). Patients undergoing silicone oil tamponade were excluded from the study. Other exclusion criteria were presence of pathologies such as macular holes, optic atrophy, glaucoma, and previous surgical intervention (other than uneventful cataract surgery performed at least 3 months prior to the procedure).

Image Acquisition

Patients who fulfilled the above diagnostic criteria were imaged using OCTA device (Optovue RTVue XR 100 Avanti, Optovue Inc., Fremont, CA, USA)at their month 3 postoperative visit. Optovue OCTA utilizes split-spectrum amplitude decorrelation algorithm (SSADA) for the acquisition of the *en face* and cross-sectional retinal images. The A-scan rate of the device is 70,000 per second and it uses a light source centered on 840 nm to obtain images of different sizes (3 × 3 mm, 6 × 6 mm, or 8 × 8 mm). The structural *en face* images allow recognition of artifacts such as shadowing and loss of signal. The OCTA images were analyzed using the RTVue software. Pre-defined automatic segmentation algorithms are available for the superficial and deep retinal vascular plexus, outer retina and choriocapillaries layer. In addition to the automatic segmentation slabs, the OCTA and OCT B-scans were manually segmented to identify additional features on the *en face* images.

In addition to the OCTA images, OCT images were also acquired for all the patients enrolled in the study. The SD-OCT images were acquired using Spectralis®, Heidelberg Engineering, Germany. The scans were performed using the high-resolution mode with 7-line raster scan and a minimum of 25 frames per second. Preoperative and postoperative color fundus photography was performed using ultra-wide field retinal camera (Optos P200Tx, Optos Inc., Scotland, UK) and/or conventional fundus camera (Carl Zeiss FF450, Zeiss Meditec, La Jolla, CA, USA) for the patients included in the study.

Image Analyses

The image analyses were performed to assess the retinal vasculature after successful retinal re-attachment. A custom semi-automated algorithm was developed and used to quantify the capillary density index (CDI) and fractal dimension (FD).[13,14] For capillary density index, all OCTA images were analyzed using a public domain software ImageJ (National Institutes of Health, USA).A circle with a radius of 1.5 mm is centered at the subfoveal region and it is divided into 4 quadrants – superonasal, superotemporal, inferonasal and inferotemporal quadrants. Using the Niblack thresholding and ROI manager, all images were binarized and converted to 8-bits with a mean pixel value and standard deviation of all points. Subsequently, the luminal area (LA) was highlighted within the circle with the brightness set to 0 and 254. The LA in the individual quadrant was merged with

the corresponding threshold area and measured using ROI manager. The CDI of each quadrant was defined as the percentage of capillary density over the stromal area at the macula region. The global CDI is the average CDI value within the 1.5 mm radius circle centering on the subfoveal region.

In addition to the vascularity indices, the central full retinal thickness (FRT) was measured by two independent graders vertically from the inner border of the retinal nerve fiber layer to the outer border of the retinal pigment epithelium on the SD-OCT scans (at the fovea). The average of the two graders' measurements was used for analysis.

Any disagreements between the graders were resolved with open adjudication. *En face* OCTA and structural *en face* images were analyzed to assess alterations in the retinal vasculature. Statistical analysis was performed using GraphPad Prism® (GraphPad Software Inc., La Jolla, CA) version 6.0. The quantitative data was expressed in mean along with standard deviations. Non-parametric tests were used to analyze the data from the study. Mann-Whitney U test was used to assess differences in TRA, LA, SA, CDI and FRT between the study and healthy eyes. All the p values were 2-sided and considered statistically significant when the values were <0.05.

RESULTS

In this study, 19 eyes of 19 patients undergoing surgery for RRD were included based upon the inclusion criteria previously mentioned. All the patients had macula "off" retinal detachment. The mean age of the patients was 40.21± 16.81 years. There were 15 males and 4 females in the study. All mean preoperative BCVA was 1.56± 1.07 LogMAR units. At the time of imaging, the mean BCVA was 0.70 ± 0.37 units (p=0.007). The mean preoperative IOP was 13.94 ± 5.8 mm Hg which increased to 20.68± 5.37 mm Hg postoperatively. OCTA imaging was performed after a mean of 4.86± 2.66 months following retinal detachment surgery. The mean duration of visual symptoms (i.e. the duration of RRD prior to surgery) was 1.76 ± 2.84 months (range: 10 days to 6 months).

Among the 19 patients included in the study, primary pars plana vitrectomy with C_3F_8 tamponade was performed in 11 eyes. 8 eyes of 8 patients underwent primary scleral buckling. All the patients included in the study had anatomically attached retinae at the time of imaging. None of the patients required re-intervention after primary surgery. There were 20 healthy subjects (control subjects) (7 females)

with no known ocular disease included in the study. The mean age of these subjects was 43.73 ± 13 years.The demographic characteristics of the subjects is listed in Table 1.

Table 1: Demographic details of patients included in the study	
Feature	Value
Mean Age (years ± SD)	40.5 ± 16.42
Male: Female	12:8
Mean BCVA (LogMAR)	1.58 ± 1.05
Mean IOP (mm Hg)	13.65 ± 5.8

En face OCTA images of the patients with RRD showed increased intercapillary spacing, reduced capillary density and decreased vascularization in the superficial and deep retinal plexuses compared to healthy control subjects. Quantitative analyses of the superficial and deep retinal plexuses were performed for the following parameters listed in the methods: TRA, LA, SA and CDI. The mean values of TRA, LA, SA and CDI for the patients and control subjects is provided in Table 2 (superficial retinal plexus) and Table 3 (deep retinal plexus). The global CDI values among patients was 33.5% and 33.69% in the superficial and deep retinal plexus, respectively, compared to 58.46% and 62.49% among healthy control subjects ($p<0.001$). The mean TCA, LA, SA and CDI were significantly lower among patients undergoing surgery for RRD compared to healthy controls. In addition, the mean central retinal thickness was also significantly lower among subjects than healthy controls.

Table 2: Vascularity Indices in the Retinal Superficial Vessels			
Region	Vascularity Index (%) Patients	Vascularity Index (%) Controls	P value*
Superior Parafovea	33.55 ± 1.4	56.90 ± 2	<0.01
Inferior Parafovea	33.33 ± 1.28	59.82 ± 2	<0.01
Nasal Parafovea	33.25 ± 1.2	57.71 ± 2	<0.01
Temporal Parafovea	33.89 ± 2.68	59.43 ± 2	<0.01
Global	33.5 ± 1.04	58.46 ± 1	<0.01
*Mann-Whitney U Test			

Table 3: Vascularity Indices in the Retinal Deep Vessels			
Region	Vascularity Index (%) Patients	Vascularity Index (%) Controls	P value*
Superior Parafovea	34.0 ± 1.95	60.45 ± 2	<0.01
Inferior Parafovea	33.1 ± 2.9	63.83 ± 2	<0.01
Nasal Parafovea	33.53 ± 2.27	61.74 ± 3	<0.01
Temporal Parafovea	34.04 ± 1.81	63.94 ± 2	<0.01
Global	34.0 ± 1.95	62.49 ± 2	<0.01
*Mann-Whitney U Test			

DISCUSSION

It is known that patients with macula-off rhegmatogenous RDs may have suboptimal visual recovery despite successful reattachment due to various reasons such as loss of photoreceptors.[7,8,10] However, microvascular changes in the macula following reattachment have not been adequately studied. Using OCTA, we evaluated the retinal microvasculature in subjects who underwent surgery for RRD.

In our study, we found that there was decreased vascularity and increased intercapillary spacing of the superficial and deep retinal layers after retinal reattachment. The results showed that patients with RRD had evidence of increased intercapillary spacing on *en face* OCTA. Mean vascularity index among patients was 33.5% and 33.69% in the superficial and deep retinal plexus, respectively, compared to 58.46% and 62.49% among controls ($p < 0.001$).

OCTA provides non-invasive high resolution imaging of retinochoroidal vascular network in subjects undergoing RRD.[12] Our findings suggest that retino-vascular changes may lead to photoreceptor damage that occurs in patients with retinal detachment. This may lead to poorer surgical outcome. Post-surgical photoreceptor degeneration and vascular alterations may also be related to the inflammation that occurs due to RRD.

The limitation of the index study is its modest sample size. Future studies with larger sample size and more structured methodology may help us improve our understanding further. In summary, patients with successful retinal reattachment may have retino-vascular changes affecting the retinal plexuses, especially the deep retinal plexus leading to photoreceptor damage and suboptimal visual recovery.

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B. Financial Disclosures

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C. Other Acknowledgements

None

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Abridged prescribing information contains only key information. For detailed information, please refer to full length Prescribing Information of OPSION® HA

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