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Proceedings

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Proceeding of the AIOC 2023 Kochi

PROCEEDINGS OF AIOC 2023 KOCHI

Proceedings of the 81st Annual Conference of

All India Ophthalmological Society

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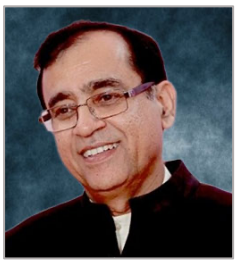

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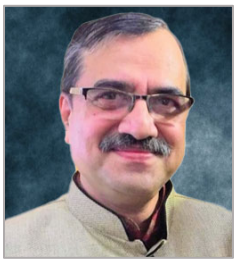

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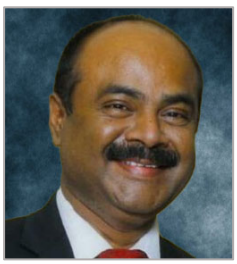

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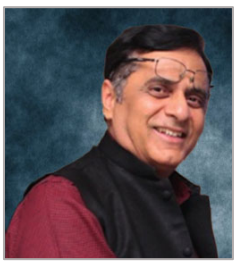

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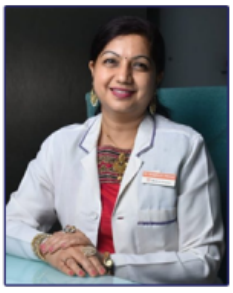

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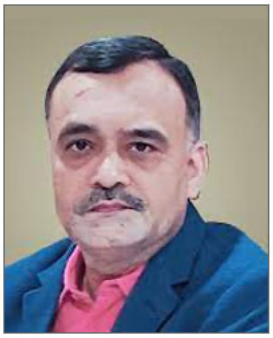

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EDITORIAL ADDRESS

Dear Members of the esteemed AIOS,

Greetings from your Editor proceedings

Dr Krishna Prasad Kudlu,

A warm hug of gratitude to all of you for giving me an opportunity to serve in the respectable and responsible capacity of Editor Proceedings. In the past 6 years, I have been working in the position of Member , Scientific committee and tried to fulfil it to the best of my abilities. There has been an overall approval of the job done and I would like to continue the good work in a better manner in my new profile.

My predecessor Dr Arup Chakrabarti has done tremendous work in the two terms that he held office and I thank him for the foundation laid to build on. Most of the scientific contents of the AIOS annual meetings are available to AIOS members at the very user friendly, easy to navigate http://proceedings.aios.org/. You can access these from anywhere in the world and improve your knowledge and scientific acumen. These priceless pearls are now at your fingertips, whatever your need be. A post graduate wanting to make a presentation, a teacher wanting to teach his pupils or a consultant wanting to make clinical decisions, AIOS ON Demand is your place top go.

We have had a successful AIOC 2023 at KOCHI and the proceedings of the same has been be brought to you after being curated and well archived. the

scientific sessions which were well received, will all be there for you to access, if you missed any. It is was an arduous task , but be rest assured you will enjoy the content in it .

Each of you will receive daily mailers which will contain heaps of knowledge for you to pick and choose . The You Tube Channel for the Editor Proceedings will also be ripe with information from the conference. Please enjoy the content and be forever hooked to the motto of "Live To Learn and Grow".

We have a very dynamic President , DR Harbansh Lal at the Helm and hope to see AIOS making great strides in his term as the captain. My Job needs all the help from the Hon Secretary which I know I will be getting, from the most knowledgeable and legendary Dr Santosh Honavar. Our enthusiastic and hard working scientific committee chairman , Dr Namrata Sharma has been delivering wonderful scientific session feasts at every AIOS conference. These ultimate scientific contents will be handed over to editor proceedings where knowledge will be delivered to AIOS members continuously through various channels.

We as a team hope to make this portal of information more beneficial to all members in my term and hope to receive all cooperation from you.

Yours sincerely

Dr. Krishna Prasad Kudlu

Editor Proceedings AIOS,

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This paper was judged as the BEST PAPER of Cataract I Session

Dr.MANPREET KAUR (K18920)

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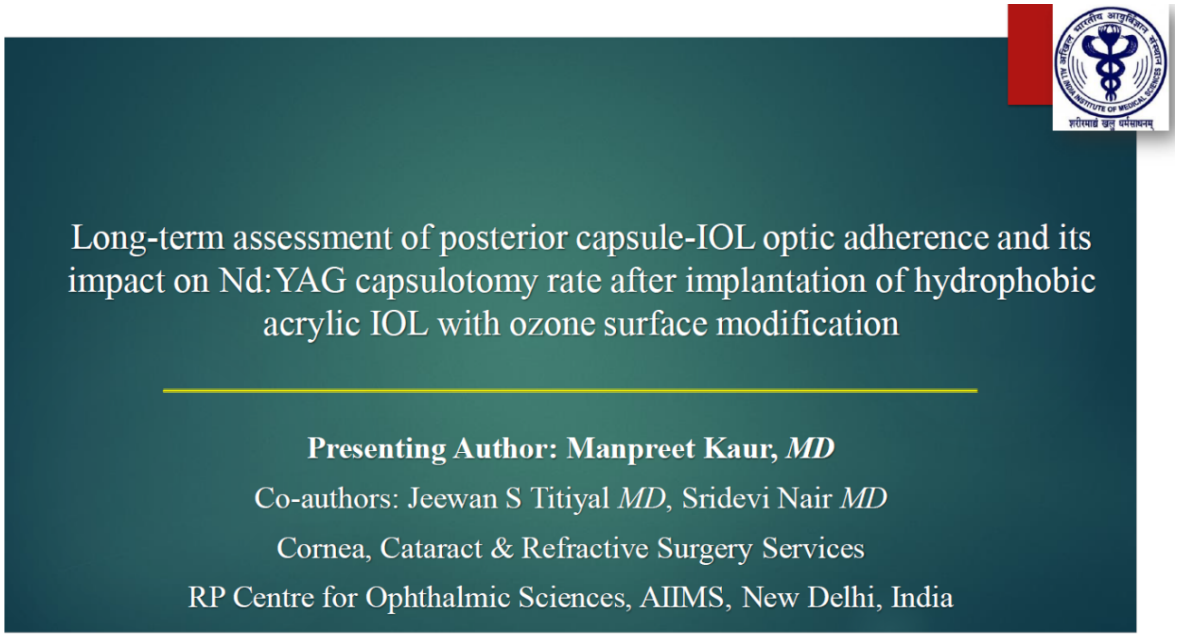
LONG-TERM ASSESSMENT OF PC-IOL OPTIC ADHERENCE AND ND:YAG CAPSULOTOMY RATE OF SURFACE MODIFIED IOL



Introduction

- **Intraocular lenses (IOL) Surface Modifications**
  - Various techniques - surface coating, covalent grafting, plasma treatment, photochemical immobilization[1]
  - Associated with enhanced biocompatibility and significant decrease in the incidence of PCO[2]
- **Vivinex XY1 (Hoya Surgical Optics, Inc.)** - Aspheric hydrophobic acrylic IOL with posterior surface modification (UV/ozone treatment)[3]
  - *Mechanism* - increased adhesion of fibronectin and lens epithelial cells (LEC) to the posterior IOL surface- promotes IOL adhesion to the posterior lens capsule and prevents PCO

Purpose of the Study

To assess PC-IOL optic adherence in surface modified IOL and impact on Nd:YAG capsulotomy rate and visual quality

1. *Huang Q, Cheng GP, Chiu K, Wang GQ. Surface Modification of Intraocular Lenses. Chin Med J (Engl). 2016;129:206–214.*
2. *Tan X, Zhan J, Zhu Y, Cao J, Wang L, Liu S, et al. Improvement of Uveal and Capsular Biocompatibility of Hydrophobic Acrylic Intraocular Lens by Surface Grafting with 2-Methacryloyloxyethyl Phosphorylcholine-Methacrylic Acid Copolymer. Sci Rep. 2017;7:40462.*
3. *Matsushima H, Iwamoto H, Mukai K, Obara Y. Active oxygen processing for acrylic intraocular lenses to prevent posterior capsule opacification. J Cataract Refract Surg. 2006;32:1035-40.*

Methods

- **Study Site**: Dr. Rajendra Prasad Centre for Ophthalmic Sciences, AIIMS, New Delhi, India
- **Study Design:** Prospective interventional study
- **Participants: Ninety-three eyes** with Immature Senile cataract grade II-IV (LOCS III) implanted with hydrophobic acrylic IOL with posterior surface ozone treatment after phacoemulsification. Cases with ocular or systemic co-morbidities excluded.

Primary Outcome Measure

- Posterior Capsule (PC) adhesion to IOL optic on Anterior Segment Optical Coherence Tomography (ASOCT) (***RTVue**, Optovue Inc., Fremont, CA)*
- Nd:YAG capsulotomy rate. Secondary outcome was visual quality.

Secondary Outcome Measures

- Visual Quality (Assessed using Ray Tracing Aberrometry)

Follow up performed on POD 1, 1 and 2 years

Results

Demographic Details

Mean Age of Patients- 59.46 ± 9.14 years

93 eyes- 37 bilateral, 19 unilateral, Male : Female= 34: 22

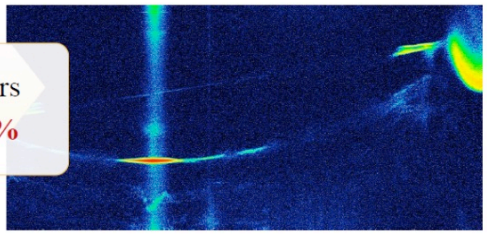
Intraoperative Course & Postoperative Visual Acuity

- No case had intraoperative posterior capsular rent or vitreous loss
- At 2 years-
  - ❖ 94.6% had corrected distance visual acuity (CDVA) 20/20 or better
  - ❖ 100% had CDVA 20/32 or better

Results

Complete PC-Optic adhesion

POD 1 **2.9%** → 1 year **67.6%** → 2 years **73.5%**



- Zhu et al. evaluated PC-optic adhesion in visual axis after phacoemulsification[1] - observed 41.5% PC-optic inadhesion at 1 day and 7.1 % at 2 months
- Used Scheimpflug imaging- less sensitive than ASOCT[2], may have underestimated PC-optic inadhesion

1. *Zhu X, He W, Yang J, et al. Adhesion of the posterior capsule to different intraocular lenses following cataract surgery. Acta Ophthalmol. 2016;94:e16-25.*
2. *Tabatabaei A, et al. Accuracy of 3 imaging modalities for evaluation of the posterior lens capsule in traumatic cataract. J Cataract Refract Surg. 2014;40:1092-6.*

Results

Visual Quality at 2 years

Visual Quality Parameter	Complete PC-Optic Adhesion	PC-optic inadhesion	P value
Strehl Ratio	0.074 ± 0.054	0.042 ± 0.023	**0.011**
MTF 5 cpd	0.552 ± 0.178	0.393 ± 0.208	**0.022**
MTF Average	0.359 ± 0.116	0.287 ± 0.082	**0.027**
RMS Total	0.546 ± 0.311	0.957 ± 0.812	**0.023**

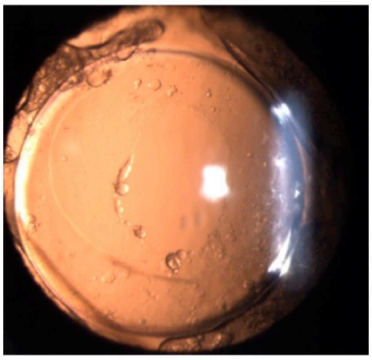
Strehl ratio and modulation transfer function (MTF) and Root Mean Square (RMS) Total aberrations were significantly better with complete PC-optic adhesion.

Residual PC-optic distance (Range 0-182 µm) positively correlated Total Higher Order Aberrations

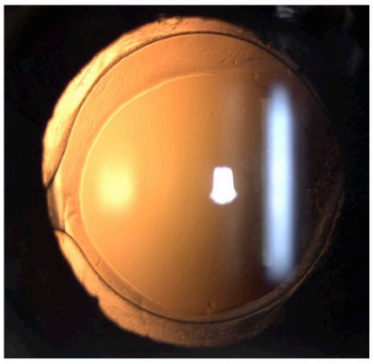
Pearson Correlation Coefficient- 0.4
p=0.03

Results

Posterior Capsular Opacification (PCO) developed in **7.5% cases** at 2 years



Peripheral PCO with clear visual axis in a case at 2 years



No PCO in 92.5% cases at 2 years

Results

PCO & Nd: YAG Capsulotomy Rates

At 2 years, PCO developed in **7.5%**

Of these, 85.7% had persistent PC-optic non-adhesion **(p=0.001)**

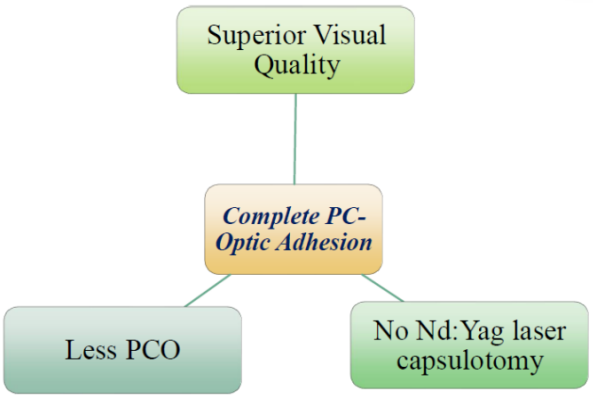
Nd:YAG capsulotomy was needed in **3.2%**

All cases requiring laser capsulotomy had persistent PC-optic non-adhesion

Conclusion

❖Surface modified IOLs expected to have higher rates of PC-optic adhesion with less PCO

❖Nearly **1/3rd cases at 1 year** and nearly **1/4th cases at 2 years** have persistent **PC-optic inadhesion**



First Study to characterize PC-optic adhesion using High-Definition ASOCT in a surface modified hydrophobic acrylic IOL

This paper was judged as the BEST PAPER of Cataract II Session

Dr. SANKET BHATNAGAR, B16754

COMPARING ACCURACY OF TORIC IOL POWER CALCULATIONS WITH AS SWEPT SOURCE OCT AND STANDARD DEVICES

INTRODUCTION

Ocular astigmatism is a refractive condition which occurs because of unequal curvatures of the cornea and the crystalline lens, decentration or tilting of the lens, or unequal refractive indices across the crystalline lens,[1] and in some cases, alterations of the geometry of the posterior pole. Several studies have reported the prevalence of corneal astigmatism in cataract patients of different age groups. In general, nearly 35%–40% of the cataract patients have astigmatism ≥1.0 D and 19%–22% have astigmatism ≥1.5 D.[2-4]

There are several ways to measure and treat astigmatism at the time of cataract surgery. Techniques to measure astigmatism include keratometry (manual or automated), corneal topography (eg, placido-based or based on the reflection of multicolour light-emitting diode [LED] points), and corneal tomography (e.g., slit-scan imaging, Scheimpflug imaging).[5] Additionally, the use of intraoperative aberrometry has been documented to improve the astigmatic outcomes.[6] However, one may not have all the diagnostic tools at their disposal and inaccurate measurements may result in post operative surprise. Thus, the purpose of this study is to compare keratometry, biometry and toric IOL power calculation and predictive accuracy between Anterion® which is a swept source OCT optimised for anterior segment imaging with Oculyzer® and IOL Master 700®

MATERIALS AND METHODS

Forty two eyes of thirty two patients presenting with age related acquired cataract and having astigmatism of > 1D between April and June 2022 were enrolled in the study. Informed consent was obtained, and the subjects' age, gender, family history, past medical history, and details of ophthalmologic surgery were recorded. The inclusion criterion was acquired cataract, astigmatic power of > 1D, clinically and topographically normal cornea with either WTR or ATR astigmatism and exclusion criteria were past history of eye surgery, and the presence of a corneal ulcer or other corneal diseases or any other ocular pathollogy10,11 All subjects were subjected to examination by slit-lamp, and direct ophthalmoscopic and retinoscopic examinations. Then the subjects underwent Auto refractometry, topography on Oculyzer®, biometery on IOL Master® 700 and Anterion® AS OCT. Surgery was performed by a single surgeon. All subjects underwent conventional phacoemulsification with Toric monofocal aspheric IOL implantation. The incision size was 2.2 mm and location was 180 degree for right eyes and 0 degrees for left eyes. IOL implanted was Alcon Acrysof ®Toric IOL with an optical a constant of 119.0. IOL power and implantation axis was calculated using Alcon online toric calculator with built in Barrett algorithm with biometry using IOL Master 700 and topography from Oculyzer. For comparison, toric power and axis was also calculated on the inbuilt Toric calculator in Anterion. The manifest refraction (MR) and keratometric values were measured at the one-month follow-up appointment, and all of the patients had a complete postoperative ophthalmic examination. Toric IOL rotation was measured using the slit lamp in one-degree steps through pupils that were dilated with tropicamide. A thin coaxial slit was projected in front of the eye and rotated until the thin slit projection overlapped with the axis marks of the IOL. MR was performed in order to evaluate residual

astigmatism. The residual corneal astigmatism that was based on the MR measurement was compared to the anticipated residual astigmatism, which is calculated using an online program. We defined the keratometric error (KE), as follows: KE = (actual postoperative astigmatism – anticipated residual astigmatism) / toricity of implanted IOL. We calculated KE using the vector calculator program VECTrAK version 1.5. Data were expressed as the mean ± standard deviation. Statistical analyses were performed using SPSS for Windows (v 11.0; SPSS Inc, Chicago, IL) using the independent samples t-test and Pearson's Chi-square test. Statistical significance was accepted at $P < 0.05$.

RESULTS

The mean age of the patients was 62.04 ± 5.14 years and the mean age of the control group was 64.4 years (P = 0.449). Male to female ratio was 20:12. Mean spherical equivalent pre operatively was 2.58 ± 1.2D. Subjects had a mean pre operative astigmatic power by refraction of 1.36 ± 0.24D, on IOL Master 700 was 1.23D ± .18D, with Oculyzer was 1.42 ± 0.54D and with Anterion was 1.32 ± 0.14D. Pre operative Mean Keratometric power measured by the different diagnostic machines in provided in Table 1. Mean K power provided by Oculyzer was higher that Anterion and IOL Master 700. Average IOL power implanted was + 22.52 ± 2.23D.

	Mean Keratometric power (D)	Standard deviation
Autorefractometer	43.25D	± 2.42
Oculyzer	44.17D	± 1.76
IOL Master 700	43.56D	± 1.81
Anterion	43.18D	± 1.23

Table 1: Mean keratometric power in Dioptres on various devices

Postoperative results are shown in Table 2. The differences between postoperative residual corneal astigmatism and the anticipated residual astigmatism are listed in Table 3. T5 IOL showed the largest differences, which were then followed by T4 and T3, although these were not significant, and to reduce the confounding factors we divided the differences by the toricities of the implanted IOL.

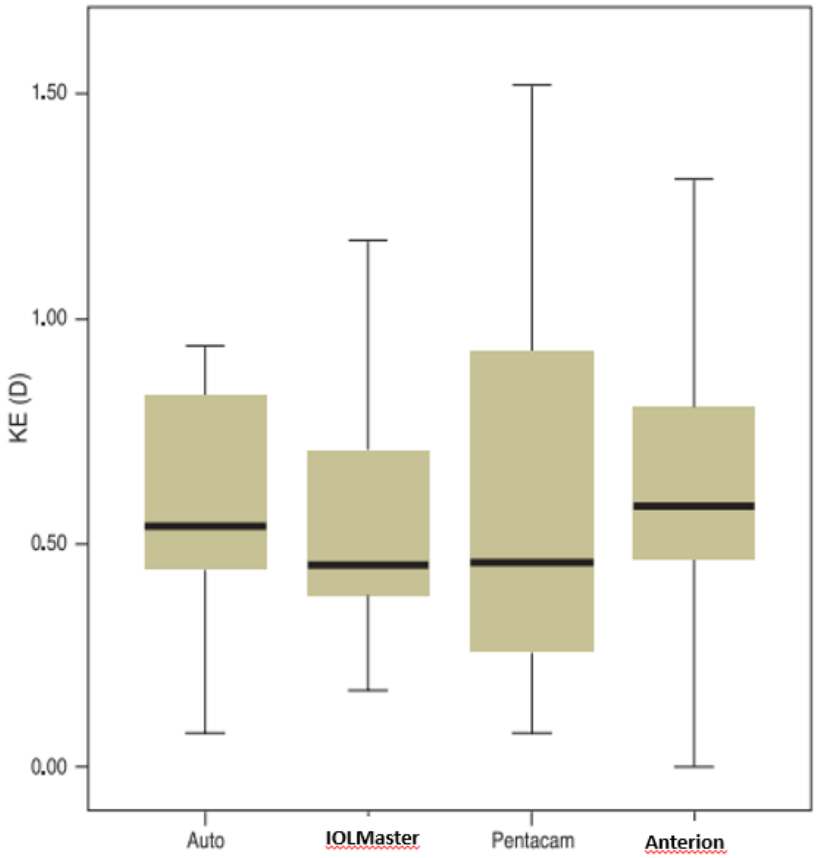
	Pre operative	Post operative day 30	p value
UCVA (logMAR)	0.57 ± 0.40	0.06 ± 0.10	0.00
BCVA (logMAR)	0.37 ± 0.30	0.007 ± 0.02	0.00
Corneal astigmatism	2.18 ± 0.67	2.34 ± 0.68	0.662
Refractive cylinder	1.44 ± 0.87	0.46 ± 0.29	0.00

Table 2: Visual acuity and manifest refraction before and three months after AcrySof toric IOL implantation

	T 3	T 4	T 5	p value
Autoref	0.63 ± 0.27	0.59 ± 0.23	0.53 ± 0.29	0.795
Oculyzer	0.60 ± 0.37	0.50 ± 0.24	0.54 ± 0.22	0.830
IOL Master 700	0.70 ± 0.49	0.59 ± 0.45	0.51 ± 0.30	0.696
Anterion	0.65 ± 0.42	0.66 ± 0.28	0.56 ± 0.16	0.856

Table 3: Comparison of the KE with regard to toricity

The average KE was 0.59 D (0.08-0.94) by the auto keratometer, 0.52 D (0.17-1.17) by the Anterion, 0.61 D (0.08-1.52) by the Oculyzer, and 0.62 D (0-1.31) by the IOL master. Although the Anterion had both the lowest average and median KE values measured, the differences were not significant between the four methods studied. All of the keratometers achieved an average KE value less than 1 D.



DISCUSSION

Preoperative keratometric data must be accurate in order to reduce astigmatism effectively when using a toric IOL. Currently in our practice we rely on multiple machines to provide keratometry and biometry. There is a need for a single imaging platform which can give us reliable and repeatable parameters for toric calculations. In our study, we used Keratometric error which is the difference between the targeted refraction and actual refraction post-surgery as a criteria to predict accuracy between the keratometers and we found out that Anterion gave the lowest mean prediction error. Also, in our study, the coefficient of reproducibility of the mean keratometric power was ±0.21 D for the auto keratometer, ±0.20 D for the Anterion, ±0.32 D for the Oculyzer, and ±0.22 D for the IOL master. All of these methods showed good reproducibility.

Shankar et al[7] have found that the corneal curvature as measured by a Pentacam showed good reproducibility, both anteriorly (mean COR, ±0.28 D) and posteriorly (COR, ±0.11 D). In our study, the COR for mean keratometric power as measured by the Pentacam was ±0.32 D, which is comparable to the results reported by Shankar et al[7]. It has been well demonstrated that the IOL Master is highly precise, accurate, and reproducible[8-10]. Kim et al[11] have demonstrated that the IOL Master has fairly good results in refractive prediction for cataract surgery. However, there have only been a few reports that have focused on keratometric accuracy. Instead, many of the previous reports have only focused on the efficacy of toric intraocular lens, but the IOL Master was often used to evaluate the preoperative keratometry, which may have indirectly validate that the IOL Master is both reliable and accurate.

However, our ability to evaluate repeatability was limited because we evaluated only the COR of the mean keratometric power. To evaluate the reproducibility of the corneal astigmatism measurements, not only should the degree of astigmatism be measured but also the axis of the astigmatism should be simultaneously evaluated by using vector analysis, or at least a separate evaluation of the reproducibility of both factors should be conducted.

Thus in terms of keratometry and biometry, Anterion proves to be reliable and reproducible, It also gives a good predictive accuracy with its inbuilt Toric calculator. Okulix, the ray tracing software evaluates refraction of rays at each optical surface is calculated using Snell's law. The calculation error inside Okulix is the same for all distances to the optical axis (residual error < 0.001D). Thus, Anterion can be used as a one stop imaging device.

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This paper was judged as the BEST PAPER of Cataract III Session

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A NEWER TECHNIQUE "SIDEWAYS SCULPTING" IN CASE OF POSTERIOR POLAR CATARACT WITH NUCLEAR SCLEROSIS.

TITLE:

Innovative method of sideways sculpting for nucleotomy in cases of hard posterior polar cataracts.

INTRODUCTION:

Posterior Polar Cataracts (PPC) have always posed a challenge for cataract surgeons due to their inherently higher propensity for posterior capsule rupture(PCR).[1] Because of possible adherence of PPC to the posterior capsule, cataract extraction carries the risk of posterior capsular breaks and the potential for vitreous loss during surgery.[2] Incidence of complication can be reduced, however, there is no surgical strategy that can completely eliminate the occurrence of PCR in a PPC. During surgery for Posterior Polar Cataracts certain precautions that need to be taken are:

1. Avoiding a large anterior continuous curvilinear capsulorhexis to ease optic capture.
2. Avoiding undue deepening or shallowing of anterior chamber.
3. Performing hydrodelineation instead of hydrodissection.
4. Avoiding rotation of the crystalline lens.

5. Maintaining low vacuum parameters and aspiration flow rate to achieve more stable anterior chamber.

6. Avoid capsular polishing.

Daljit Singh classification of posterior polar cataract[3] is being followed:

Type 1: PPC associated with posterior subcapsular cataract.

Type 2: Round or oval discoid opacity with a ringed appearance like an onion with or without grayish spots at the edge.

Type 3: Round or oval discoid opacity sharply defined with dense white spots at the edge often associated with weak, thin, or absent posterior capsule. The white dense spots are a diagnostic sign (Daljit Singh sign) of posterior capsule rupture or extreme thinning.

Type 4: Combination of the above 3 types with nuclear sclerotic cataract

OBJECTIVES:

To introduce an innovative method of "sideways sculpting" for nucleotomy in cases of hard posterior polar cataracts.

MATERIAL AND METHOD:

Study design:

This was a retrospective analysis conducted at a tertiary eye care hospital.

Ethics approval: The institutional ethical committee approval was obtained before the initiation of the study.

Inclusion criteria: Posterior Polar Cataract with nuclear sclerosis of grade 2 and above were included.

Exclusion criteria: Softer grades of cataract and nuclear sclerosis of less than grade 2 were excluded.

Study period: Data over a period of 4 years.

Sample size: 17 eyes of 17 patients with posterior polar cataract (PPC) surgery.

METHODOLOGY:

Patients satisfying the inclusion criteria were included in the study. Single surgeon performed all the surgeries. Hard posterior polar cataract with nuclear sclerosis grade2 or higher were subjected to a newer surgical technique. After initial incisions and the continuous curvilinear capsulorhexis (CCC) was completed, controlled hydrodelineation was performed to separate the endonucleus from the epinuclear shell. Nucleofractis is performed by trenching in the mid-line vertically and then creating horizontal grooves by moving the phacotip sideways creating a "+" or sideways nucleofractis without rotating the nucleus. Phacoemulsification was performed by pulling out each fragmented nuclear quadrant, maintaining the integrity of the epinuclear portion of the crystalline lens and chopping the fragmented nuclear quadrants. Intraocular lens was implanted in the bag.

STATISTICAL ANALYSIS:

The data was collected, pooled, subjected to appropriate statistical analysis and conclusions were drawn

RESULTS:

The cases were uneventful and without any complication. In one case there was small opening in posterior capsule. The nucleus and epinucleus were easily removed from the compromised posterior capsule in one of the seventeen cases using the sideways sculpting technique without posing any additional risks. IOL could be implanted in the bag. The remaining cases were uneventful and without any complication. It is a helpful technique for harder grades of cataracts because the nucleus must be divided, as opposed to softer grades of nuclear sclerosis where the nucleus can be aspirated without dividing. This simple and clean process disassembles the nuclear chunk,

making room for the remaining fragments to be separated. The posterior capsule is protected by the remaining epinuclear cushion, reducing the likelihood of severe intraoperative complications. A “sideways sculpting” nucleofractis technique ensured safety and familiarity. This procedure reduces anticipated intraoperative and postoperative complications while also making the surgery easier. The goals of performing phacoemulsification in eyes with PPC are to maintain the barrier of the irido-zonular-capsular diaphragm between the anterior and posterior segments and to implant an intraocular lens (IOL) in the bag is achieved with this technique. This surgical technique provides nuclear separation and emulsification without distorting or exerting traction on the weak posterior capsule, within the cushion of the epinucleus which protects and tamponade the posterior capsule. Closed chamber is maintained without distorting the capsular bag. Contours of the cornea and the globe are maintained and risk of intraoperative PCR is reduced in eyes with PPC.

DISCUSSION:

This study was undertaken to investigate the effect on harder grades of cataracts because the nucleus must be divided, as opposed to softer grades of nuclear sclerosis where the nucleus can be aspirated without dividing. This technique helps in nucleus division without nucleus rotation. The goal of performing phacoemulsification with this technique in eyes with PPC is to prevent, delay or minimize the complication.

CONCLUSION:

We arrive at a conclusion that this is an innovative surgical technique provides nuclear separation and emulsification without distorting or exerting traction on the weak posterior capsule. This is a useful technique for PPC with nuclear sclerosis grade 2 and more.

LIMITATIONS:

Our study is descriptive, non-comparative and retrospective in nature. Another limitation of our technique is that we cannot apply it to soft PPC cataracts.

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This paper was judged as the BEST PAPER of Community / Social Ophthalmology - I Session

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TECHNICIAN AND TELEOPHTHALMOLOGY ASSISTED ROP SCREENING IN RURAL TAMILNADU AND ANDHRA PRADESH

SYNOPSIS

Project Vision on Wheels was started in 2018, to identify the babies in Rural Tamilnadu with Retinopathy of Prematurity (ROP) by the Neo fundus camera. Total number of babies screened from June 2018 to December 2021 was 18,117. In 2019, 2020 and 2021, 279, 244 and 351 babies underwent laser. There was a yearly increase in the number of babies with treatable ROP needing laser in the 750-1000 gm category (8%, 11%, 15% and 11 % in 2018, 2019, 2020 and 2021 respectively) and decrease in the >2000 BW category (6%, 7%, 1% and 1% in 2018, 2019, 2020 and 2021 respectively). These findings of decreasing treatable ROP in bigger and more mature babies and increasing treatable ROP in younger babies, over time can be attributed to the success of a committed screening strategy such as that of project Vision on Wheels. This paper presents the largest data till date (according to MEDLINE search) of ROP detected by Neo in the rural areas in the twin states of Tamilnadu and Andhra Pradesh.

Retinopathy of Prematurity (ROP) is a blinding disorder affecting preterm babies, with India accounting for a major portion of the cases worldwide. In India, ROP affects the babies of underprivileged parents, especially in rural

areas, but the incidence is largely unknown. Project Vision on Wheels was started in June 2018, to identify the babies in Rural Tamilnadu and Andhra Pradesh with ROP by a handheld retinal camera, the "3nethra Neo" (Neo), and to ensure their prompt treatment with laser. This paper presents the 3 ½ year data of the project from June 2018 to December 2021, and includes the incidence of ROP and the characteristics of the babies requiring laser according to birthweight (BW), Gestational age (GA) and Postconceptional age (PCA).

MATERIALS AND METHODS:

The total number of babies screened from June 2018 to December 2021 was 18,117. Of these, 1051 babies were identified to have treatable ROP and 1046 babies underwent laser. Early Treatment of Retinopathy of Prematurity (ETROP) guidelines were used for laser.[1,2] Amongst the lasered babies, 516 were male and 530 were female. In 2018, 177 babies were found to have treatable ROP of which 172 underwent treatment. In 2019, 2020 and 2021, 279, 244 and 351 babies were found to have treatable ROP respectively and all babies underwent laser. The majority of lasered babies were in the 1000-1500 BW and 31-35 GA and 36-40 PCA categories in all the years. There was a yearly increase in the number of babies with treatable ROP needing laser in the 750-1000 gm category (8%, 11%, 15% and 11% in 2018, 2019, 2020 and 2021 respectively) and decrease in the >2000 BW category (6%, 7%, 1% and 1% in 2018, 2019, 2020 and 2021 respectively) in the number of babies with treatable ROP needing laser. In 2019, 11% of babies with treatable ROP were in the >35 GA category, while the percentage fell to 7% and 9% in 2020 and 2021 respectively.

Table 1: Total number of babies screened and lasered year wise

Total No. of Babies	2018	2019	2020	2021
Screened	1582	5616	5277	5642
Advised laser	177	279	244	351
Underwent Laser	172	279	244	351

Table 2: Year wise distribution of lasered babies according to birthweight

Birthweight	2018	2019	2020	2021
<750 gms	2	2	1	6
750-1000 gms	15	31	37	41
1001-1500 gms	94	97	133	203
1501-2000 gms	21	66	43	72
>2000 gms	11	21	4	6
NA	29	62	26	23

NA: Data not available.

Table 3: Year wise distribution of lasered babies according to GA

GA	2018	2019	2020	2021
≤ 28 wks	11	25	28	37
29-30 wks	25	38	29	82
31-35 wks	87	124	132	175
>35 wks	15	31	17	34
NA	34	61	38	23

NA: Data not available.

Table 4: Year wise distribution of lasered babies according to PCA

PCA	2018	2019	2020	2021
≤ 30 wks	0	0	0	3
31-35 wks	45	67	45	99
36-40 wks	82	107	82	178
41-45 wks	9	41	77	44
>45 wks	2	3	2	4
NA	34	61	38	23

NA: Data not available.

DISCUSSION

"3nethra Neo" was used for the retinal imaging of infants in this study, its safety and efficacy having been well established earlier.[3] The majority of babies requiring laser in Project Vision on Wheels belonged to the 1000-1500 gm BW category (527/1046, 50%). However, there was a substantial percentage of babies in the higher birth weight category as well (1501-200gms: 202/1046, 19% and >2000 gms: 42/1046, 4%).

On a similar note, the majority of babies requiring laser belonged to the relatively higher GA and PCA groups (31-35 wks GA: 518/1046, 49.5%; 36-40 wks PCA: 449/1046, 43%). However, there was a substantial percentage of babies in the higher GA category as well (> 35 wks GA: 97/1046, 9% and 41-45 wks PCA: 171/1046, 16%, > 45 wks PCA: 11/1046, 1%). This is commensurate with the Indian experience of ROP occurring in bigger birthweight and higher gestational age babies.[4,5]

There was this important finding of decreasing treatable ROP in bigger and more mature babies and increasing treatable ROP in younger babies, over time, that was discovered on analysis of the data. This could be attributed to the success of a committed screening strategy such as that of project Vision on Wheels in reinforcing good neonatal care in the rural areas. This paper presents the largest data till date (according to MEDLINE search) of ROP detected by RETCAM in the rural areas in the twin states of Tamilnadu and Andhra Pradesh.

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This paper was judged as the BEST PAPER of Community / Social Ophthalmology - II Session

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SMARTSCOPE KIT : A PORTABLE EYE HOSPITAL FOR SCREENING IN OUTREACH CAMPS

Eye screening camps fulfils the main purpose of providing high volume, high quality and low-cost eye care service to rural population of the target area through mobile camps that are accessible, affordable and appropriate. Conventionally, ophthalmologists use torchlight and direct ophthalmoscope for screening of ocular diseases. We conducted eye screening camps with the help of only a smartscope kit which included smartphone based innovative anterior-posterior segment, cobalt blue, gonioscopy, KOH microscopy imaging tools which helped us in diagnosing cataracts and various ocular diseases; easy referrals to base hospital for further management. 20 camps including 2315 patients were screened with the help of smartscope kit through which we diagnosed – 1454 cataracts, 7 fungal corneal ulcer, 3 foreign body of cornea, 17 primary angle closure suspects, 42 diabetic retinopathy, 8 retinal detachments, 9 iris colobomas with retino-choroidal colobomas, 2 macular holes, 1 ICE syndrome with PAS on gonioscopy, 1 CRAO, 3 corneal tears, 4 uveitis, 3 vitreous haemorrhage, 2 OSSN, 3 neovascular glaucoma cases. It is the only study with large volume community screening done with only smartphone based frugal do it yourself

tools. Smartscope kit is a new age community screening kit with near perfect compared to slit lamp diagnosis of ocular diseases and also helpful in early diagnosis and prompt treatment, documentation, immediate referral and point of care diagnostics.

INTRODUCTION

WHO (world health organization) identifies and prioritizes affordable health care for universal health coverage. A cataract is the leading cause of reversible blindness and few countries have successfully tackled the problems to access affordable eye care.[1,2,3] In countries like India, fight against the blindness is achieved through regular outreach camps. Acquiring instruments like slit lamps or I.O. (Indirect Ophthalmoscope) for examinations and mobilizing these expensive instruments is a challenge in outreach camp. It is not practically possible in countries like India. We need more frugal and easily mobile instrument to screen patient for diseases. Here we described smartphone kit in which all the instruments are smartphone based, and we can use these instruments in outreach camps.

METHODS

A prospective study has been done. We collected the data of 180 eye camps done across 6 months in 3 states – Tamilnadu, Karnataka, Kerala. Patient attending the outreach camps were included in the study regardless of their lens status. All the patient underwent examination using smartphone based instruments from the smartscope kit.

THE SMARTSCOPE KIT CONSITIS OF

1. Trial frame, pin hole, +10d lens
2. Smartphone visual acuity charts – recording visual acuity, ischiara chart, contrast sensitivity chart

3. Anterior Segment Photography with Intraocular lens (ASPI) : for anterior segment evaluation
4. Anterior Segment Photography with Intraocular lens gonioscopy (ASPI-gonio) : for anterior chamber angle evaluation
5. Trash To Treasure Retcam : for posterior segment evaluation
6. Smartphone COaided cObalt Blue photography DO it yOurself (SCOOBY DOO) : for cobalt blue photography to detect epithelial defect, seidels test, dry eye etc
7. IOLSCOPE : to detect fungal hyphae from corneal scrapping and parasite from lid/conjunctiva etc
8. Schiotz tonometer : to screen for IOP
9. Kimuras spatula / 11 blade
10. Gloves, cotton swab, fluorescein strips, eye patch, dilating and anesthetic eye drops

Patient were then grouped into their respective specialties for treatment – cataract, cornea, glaucoma, paediatrics, retina and were referred to the base hospital.

RESULTS

20 camps including 2315 patients were screened with the help of smartscope kit through which we diagnosed – 1454 cataracts, 7 fungal corneal ulcer, 3 foreign body of cornea, 17 primary angle closure suspects, 42 diabetic retinopathy, 8 retinal detachments, 9 iris colobomas with retino-choroidal colobomas, 2 macular holes, 1 ICE syndrome with PAS on gonioscopy, 1 CRAO, 3 corneal tears, 4 uveitis, 3 vitreous haemorrhage, 2 OSSN, 3 neovascular glaucoma cases.

DISCUSSION

Outreach camps for cataract surgeries has been introduced under the district board of control of blindness society (DCBS) to provide vision to the population suffering from avoidable blindness. It forms the main backbone of providing treatment in developing countries like India to poor people who cannot afford this surgery otherwise. It has helped the country achieve and provide vision which would have been impossible otherwise. The main basis of outreach camps done by many eye hospitals of our country is to screen cataract with the help of basic instruments like torch light and to view the posterior segment by the direct ophthalmoscope. In such circumstance we tend to miss other important co existing eye diseases. We used the Smartscope kit for the camps we screen to diagnose many different coexisting diseases which were referred to the main center for further management. Ophthalmic equipment is a big investment for any health care facility that needs protection and regular maintenance.[7] The total cost of the solution we are describing is within Rs 10000, which makes it affordable in low to middle income countries. Outreach camps which is a common ophthalmic practice in the Indian subcontinent could benefit from this cost-effective technique. It enables ophthalmologists to accurately detect and manage ocular comorbidities which improve diagnosis and screening of disease hence enabling better outcomes. It is the only study which uses frugal ophthalmic imaging devices and an easily available device like smartphones which can change and modify modern eye screening trends in the country. This office based rapid screening kit with the help of an instant image by the smartphone can influence the patient to obtain prompt treatment by showing the video/photo of the problem. These tools can be used by medical staff with minimal skills in remote, rural setups devoid of slit lamp bio-microscopy and laboratory setups. It can also help in case discussions, treatment opinion, publications and photo documentation in rural and

emergency setups devoid of slit lamps. It also helps **us to triage cases in camps to refer them to base hospital.**

CONCLUSIONS

Outreach camps are backbone to deliver eye care facilities in developing countries like India. Mostly eye camps are for screening the cataract. But by the use of our smartphone kit we are trying to diagnose the eye diseases other than cataracts. This is really helpful for rural area population, because they never come voluntarily for eye checkup. This aims in secondary prevention – "Early diagnosis and Early Treatment". We are trying to implement this plan of action in almost every camp. So that we can serve most of the rural population. These are cost effective and easily portable devices in camps.

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This paper was judged as the BEST PAPER of Community / Social Ophthalmology – III Session

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HOMECARE AS A COMPLIMENTARY EYE CARE DELIVERY MODEL DURING AND AFTER COVID-19 PANDEMIC

We as children, have either heard from parents or grandparents about the family physician who was only a telephone call away. The mushrooming of specialist and super speciality centers was possibly the death knell for the family physician. In the era of the diabetologist (read super-super specialist), do we care about the general practitioner who knows all but not enough for many? General practitioners of yesteryears provided the nearby go-to healthcare facility for one and all. Family physicians reached out to the homebound – the last mile. An increase in population would mean an increase in the requirement for eye health care. Additionally, the eye care services are not fairly distributed. There are many urban underprivileged of society, geriatric centres, and domiciliary patients in and around the city. The program can cover specific areas as scheduled on a regular basis. It would be a self-sustaining module with a balance between paying patients and serving of the economically underprivileged,

COVID-19 forced us to introspect and has been a catalyst for change in health care strategy.[1,2] During COVID there has renaissance of the teleophthalmology and home care delivery model. Several factors may have

been responsible for this welcome change – better technology (smartphones), improvised imaging systems, travel restrictions and the need to deliver care to the elderly or home-bound patients who were at an increased risk of COVID 19.[3,4] Neuro-ophthalmology services have used teleophthalmology platforms extensively.[5] Most participants (97%) of telemedicine favour using this digital tool again to seek medical advice.[6] HomeCare platform consisted of a home visit to record multiple datapoints – vision, intraocular pressure, refractive correction for glasses where needed and images of the eye and retina. These data-points are made available to the eye doctor. A video consultation between the patient and eye doctor on ConnectCare - teleophthalmology platform of L V Prasad Eye Institute enables the eye doctor to diagnose and treat the eye disease. Telemedicine platforms have compared well with face-to-face patient-doctor interactions.[7-9] Apart from the objectives to develop a horizontal, it can be linked with primary health care and provide awareness, education on issues related to eye care in the community. The other core activities that will be part of the program can be summarized by "*3 R's*":

- Recognition of common blinding conditions
- Refraction and dispensing of glasses
- Referral to higher levels of eye care,

METHODS

Home Care service makes eye care available to all who cannot reach us. This includes field team - vision technician or optometrist who visits the home of patient and records data points – visual acuity, intraocular pressure, anterior and posterior segment photographs. These data points are accessed by the eye doctor over home care app connected to electronic medical record system. The eye doctor is located at the telecommand centre, who on video

call with patient and attendant discusses and recommends glasses, medicines and if necessary, investigation and/or surgery.

Home care service offers several unique features to make it sustainable:

- Trained Vision Technician will do the home visit to record vision, capture images with hand held equipment and prescribe glasses.
- Images on Electronic Medical Records help eye doctor to make diagnosis and plan management.
- COVID safety protocols are followed through the pandemic.
- Electric scooters for transport will improve reach to each corner of the city within 50 km radius.
- Electric scooter gives easy accessibility to reach interiorly located homes
- Electric-driven transport will be a futuristic green initiative and help save cost.
- Post-COVID, the home care service continues to reach the urban poor, home-bound elderly and patients needing bedside eye care.
- Cross-subsidized model of treatment enables a sustainable, long-term, robust, economically viable model which will enable home visits to the economically underprivileged at no cost to the patient.

RESULTS

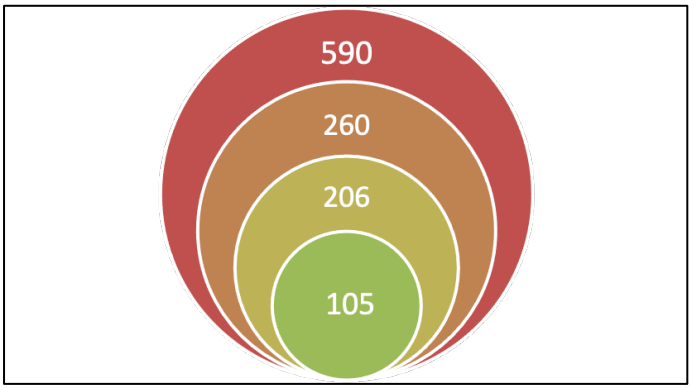
A total of 590 patients received HomeCare service between August 2020 and January 2023. Of these 426 were new patients and 164 had opted for Homecare as follow-up visit.

Based on age groups, out of 590, 260 were >60, 206 were >70, and 105 were >80 (Figure 1).

Among the> 70-year elderly group, 69 had cataract and anterior segment disorder, 33 had glaucoma, 28 had retinal disorder, and 15 had plasty (Figure

2). Female predominated HC with 353 opting for this service compared to 237 male patients (Figure 3).

Figure 1: Distribution of patients who received HomeCare based on age



Total Number of patients seen through HomeCare=590

Total Number of patients seen through HomeCare >60years=260

Total Number of patients seen through HomeCare > 70years=206

Total Number of patients seen through HomeCare >80years=105

Figure 2: Gender Distribution of Homecare patients

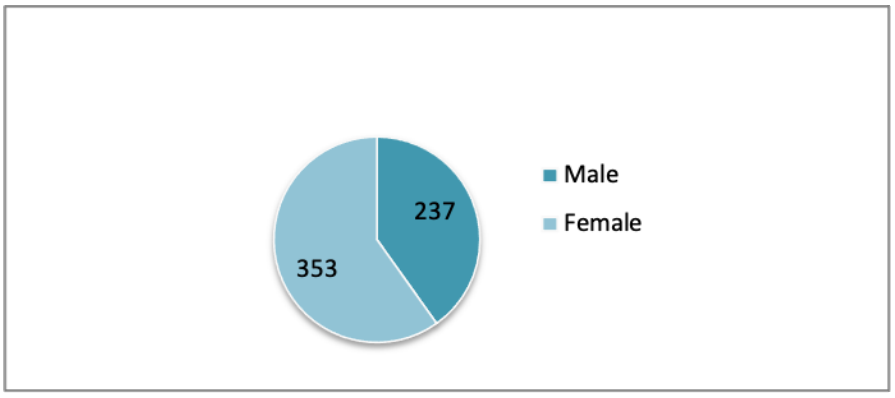
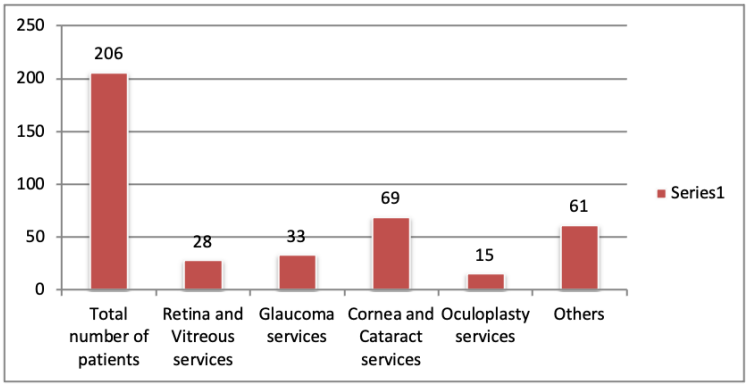


Figure 3: Distribution of HomeCare patients>70years based on their diagnosis



DISCUSSION

Home Care platform emerged as a powerful tool during and after the COVID-19 pandemic.

COVID-19 made access to health care difficult, especially for the elderly and vulnerable individuals.

Highlights of the experience rendered under homecare included:

1. The elderly, defined as those above 70 years, were beneficiaries for 35% of patients. Half of these were > 80 years of age. This tends to show that homecare services were found particularly suited for elderly patients.
2. Females predominated the patients among homecare beneficiaries. This was possible because they were more likely to be available at home compared to their male counterparts.
3. Homecare services were availed for varied types of ocular disorders ranging from anterior segment disorders, glaucoma, posterior segment and oculoplastic disorders.

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PMID: 34383722.

This paper was judged as the BEST PAPER of Community / Social Ophthalmology – III Session

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IHOPE: AN INNOVATIVE BADGE-OF-HOPE CHILD-LIFE PROJECT FOR CHILDREN WITH RETINOBLASTOMA

PURPOSE:

Innovative approach to yield higher compliance in children with retinoblastoma based on incentive theory of motivation.

METHODOLOGY:

A prospective study of 100 patients with retinoblastoma with pre and post intervention questionnaire based analysis wherein treatment based badges of courage where distributed.

RESULTS:

Among 100 retinoblastoma children a total of 630 badges were distributed. Cost was INR90 per child. Treatment-based badges for all retinoblastoma modalities were given over 3 months. Increase in compliance was noted along with parent satisfaction. Improvement was documented based on psycho-social aspects. Overall, there was improvement in all variables showing excellent response and effective intervention.

CONCLUSION:

Positive motivation yields higher compliance especially in children. The journey of these children from being fighters to survivors can be made more

interesting and joyous by introducing child-life projects that focus on psychosocial aspects.

KEYWORDS:

Community Ophthalmology, Retinoblastoma, Child-life project, Non-governmental Organization

INTRODUCTION:

Retinoblastoma (Rb) is a life-threatening childhood malignancy which is treatable based on the currently available treatment modalities and international treatment protocols. However, the entire process of treatment takes a toll on the child, parents and the entire family physically, mentally and emotionally. Several psychological assessment studies have quoted that positive motivation yields higher compliance in children.[1]

Therefore, an innovative concept was designed to assess the effect of the "Incentive theory of motivation",[2,3] on these children, to increase involvement and encourage the Rb patients from being Fighters to Survivors.

METHODOLOGY

The project was carried out at a super-specialty ocular oncology setup as a pilot study where the children being treated actively for retinoblastoma were included. It was a questionnaire based study conducted over 3 months to assess compliance to treatment among children along with parent satisfaction.

Improvement was documented based on psycho-social aspects like

- readiness to go to hospital
- post-treatment mood
- knowledge about disease
- interaction with peers
- food intake

- sibling interaction
- parent feedback about the project.

Being a pilot study, a mark of 100 children was kept for analysis of efficacy and outcome. Under this project the children were provided a sash along with circular assorted badges according to the different phases /stage of Rb treatment as an incentive with an aim to focus on increased treatment compliance in the Rb patients. The treatment-based badges were as per the individually followed protocol i.e. for intra-venous chemotherapy, peri-ocular topotecan, intra-vitreal topotecan, bone-marrow aspiration, cerebro-spinal fluid analysis, intra-arterial chemotherapy, cryotherapy, trans-pupillary thermotherapy, enucleation, safety-enhanced cataract surgery, plaque brachytherapy, external beam radiation therapy and for tumor regression.

The project design included provision of a neckerchief with a golden badge to children who have successfully fought the disease and survived with pride. A social worker was also provided for counselling the parents and catering to their queries related to the Rb treatment.

The project was carried out with the funding contributions by a non-governmental organization CaKids KidsCan and the second phase of the pilot study is to take this project pan-India across all the Fight Rb India stake-holders group for a wider out-reach.

RESULTS

Among 100 retinoblastoma children a total of 630 badges were distributed. Cost was INR 90 per child. Treatment-based badges for all retinoblastoma modalities were given over 3 months. Increase in compliance was noted along with parent satisfaction. Improvement was documented based on psycho-social aspects. The change in knowledge about the disease did not

show any significant change, however other variables showed an improvement amongst all the cases, showing excellent response thus proving it to be an effective intervention.

CONCLUSION:

Positive motivation yields higher compliance especially in children. The journey of these children from being fighters to survivors can be made more interesting and joyous by introducing child-life projects that focus on psychosocial aspects.

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This paper was judged as the BEST PAPER of Comprehensive Ophthalmology Session

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EFFECT OF DIMS LENSES ON HALTING THE PROGRESSION OF MYOPIA NOT RESPONDING TO LCA (0.01%) EYE DROPS

ABSTRACT

Objective:

To assess the effect of DIMS (Miyosmart) lenses on myopic progression in children not responding to low concentration atropine (0.01%) eye drops

Methods: 10 children not responding to LCA (0.01%) eye drops were advised to start using Defocus Incorporated Multiple Segment (DIMS) lens to halt the progression of myopia. The children were followed for a period of 1 year.

Results: 8 out of 10 children did show reduction in progression of myopia. Pre DIMS the progression was -0.68 D +/- 0.3 D sph which reduced to -0.24 +/- 0.2 diopter progression post DIMS lens in the 8 children. The remaining two children still progressed by -0.57 +/- 0.4 D sph over a year. The axial length growth reduced from 0.28 +/- 0.3 mm to 0.16 +/- 0.2 mm after using DIMS lens in these non responders

CONCLUSION:

The DIMS lens does show initial promise in reducing the progression of myopia even in children not responding to LCA 0.01% eye drops.

Low-concentration atropine (LCA; 0.01%) has become the cornerstone for the treatment of myopic progression.[1-7] Few reports from India by Jethani and Dave[8-11] and Saxena et al. [12] do suggest that LCA is efficacious in preventing the progression of myopia in Indian children.[8-12] Smith et al [13] described the peri macular area being responsible for ocular growth and s spectacle design of peripheral defocus which helped preventing myopic progression [14]. The patients who are myopic and/ or have parental history of myopia are morelikely to have peripheral hyperopc defocus.[15] However, in Indian eyes there has been asymmetry of this decous in nasal and temporal retinae.[16] Defocus Incorporated Multiple Segments (DIMS) spectacle lenses [16-21] were made to create a myopic defocus and have been known to slow down the progression. However, the role of these lenses in children who are non responder to atropine ais not known, We did a study to assess the effect of DIMS (Miyosmart, Hoya) lenses on myopic progression in children not responding to low concentration atropine (0.01%) eye drops.

MATERIALS AND METHODS

The study was approved by Institutional review board. The non responder was a child who was using low concentration atropine 0.01% eye drops and was progressing -0.5 per year or 0.3 mm axial length per year. Subjects with less than 75% compliance rate (5.25 days/week) were not included in the study. The primary end point was myopia progression over 1 years. The baseline was taken after 14 days of starting, and myopic progression was calculated from this reading.

This was a single arm non randomised prospective interventional study involving 10 children not responding to LCA (0.01%) eye drops and were

advised to start using Defocus Incorporated Multiple Segment (DIMS) lens to halt the progression of myopia. The children were followed for a period of 1 year.

OBSERVATIONS

The mean age was 8.4 +/- 2.1 years. A total of 8 children show reduction in progression of myopia. Before the atropine eye drops were started in these children the progression was -0.76 +/- 0.4 D sph per year and the axial progression was 0.32 mm +/- 0.1 mm in the year before atropine eye drops were started.

The reduction in progression was seen with low concentration atropine but it was still higher than -0.5 D per year. Pre DIMS the progression was -0.68 D +/- 0.3 D sph which reduced to -0.24 +/- 0.2 diopter progression post DIMS lens in the 8 children. The remaining two children still progressed by -0.57 +/- 0.4 D sph over a year. The axial length progression also reduced from 0.28 +/- 0.3 mm to 0.16 +/- 0.2 mm after using DIMS lens in these non responders to LCA drops.

	Refraction	Axial Length
Mean Sph Equivalent	-3.9 +/- 2.3 D	
Pre atropine progression	-0.76 +/- 0.4 D	0.32 +/- 0.1 mm
Pre DIMS Progression	-0.68 +/- 0.3 D	0.28 +/- 0.3 mm
Post DIMS Progression	-0.24 +/- 0.2 (n=8)	0.16 +/- 0.2 mm

Two patients progressed -0.57 +/- 0.4 D sph and 0.24 +/- 0.2 mm. Taking these two along the mean progression for all 10 children was -0.39 +/- 0.5 D The peripheral refraction was found to be

	20^0 Temporal	Central	20^0 Nasal
Mean refraction	-3.1 +/- 2.4 D	-3.9 +/- 2.3 D	-3.2 +/- 3.1 D

DISCUSSION

The use of LCA (0.01%) eye drops to prevent the progression of myopia in school-going children is one of the common treatment of choice. However, there are children who do not respond to LCA 0.01% and although the percentage is variable it could be anywhere between 20-55% of children. There have been reports about usage of higher concentrations of atropine. However, the higher concentration of atropine may suffer from the adverse effects like increase in size of pupil causing photophobia, reduced accommodation leading to receded near point of accommodation etc.

Peripheral hyperopic refraction has been thought to contribute in growth of the eyeball in macque monkeys in experimental studies. [13] Since the size of myopic eye has axial progression, the myopic eyes are differently shaped than hyperopic eyes. The emmetropic retinae were oblate but this reduced as the myopia progressed and the myopic eyes had a more pointed shape. [22] Koomson et al measured 30^0 nasal and 30^0 temporal refraction in patients with myopia and with or without parental myopia. They found that young myopic adults with positive parental myopia had both increasing axial length and increasing peripheral hyperopic defocus as compared to their counterpart with negative parental myopia. [14] The difference in peripheral refraction was more than 0.75 D. This was however not seen in a study on Indian eyes by Yelagondula et al [15] who found that although the temporal retinae showed peripheral hyperopic defocus, the nasal retinae actually showed myopia defocus in children with progressive myopia.

To counter this peripheral hyperopia, DIMS spectacles have been tried and tested for reduction in progression of myopia in last few years. [16-21] Lam

et al [18] published their randomised trial for comparison of DIMS versus single vision (SV) lenses and found that myopic progressions over 2 years were -0.41±0.06 D in the DIMS group and -0.85±0.08 D in the SV group. Mean axial elongation was 0.21±0.02 mm and 0.55±0.02 mm in the DIMS and SV groups. They followed up this study and the children who had worn DIMS lenses continued to wear DIMS lenses (DIMS group), and children who had worn SV lenses switched to wear DIMS lenses (Control-to-DIMS group). [20] They reported a slowing down in the axial elongation of children in DIMS group by 62% than those in the SV group. In their study group, 21.5% children who wore DIMS lenses had no myopia progression over 2 years, but only 7.4% for those who wore SV lenses.

In the followup study of 6 years, they had four groups. [21] Lam et al study is mainly on either DIMS or Single vision lenses. Their study has Group 1 who wore DIMS spectacles as a primary treatment for 6 years, the second Group 2 which wore DIMS lens for the first 3.5 years and then SV spectacles afterwards for the rest of 2.5 years. The Group 3 which wore SV spectacles in the first 2 years and later switched to DIMS and the Group 4 wore SV spectacles in the first 2 years, switched to DIMS for 1.5 years and then SV spectacles again. [18,20-21] It was obvious from their studies that DIMS glasses do slow down the myopic progression and the rebound effect is not significant. The selection bias where the subjects can choose to discontinue the spectacles is one the major limitation in these studies

DIMS lenses have not been tried in non responders to atropine in conjunction with atropine. In a recent study by Kaymak et al [17], they proved the safety of using these glasses in conjunction with LCA atropine eye drops. They proved the safety of these glasses in mesopic conditions. In our study the children who were included didn't respond to atropine but the rate of progression did slow down after using atropine. So it was imperative to try

and add DIMS as a complimentary treatment to low concentration atropine rather than use it as a supplementary treatment.

The children were already on atropine for at least one year before DIMS glasses were started. Although the rate or myopic progression reduced, it was still significant to try out another therapy. In conjunction, the rate of myopic progression was below 0.5 D per year in 8 out of the total 10 children.

Conclusion

The DIMS lens does show initial promise in reducing the progression of myopia even in children not responding to LCA 0.01% eye drops when given in conjunction with atropine eye drops.

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This paper was judged as the BEST PAPER of Cornea – I Session

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CLINICAL OUTCOMES OF CORNEAL NEUROTIZATION USING SURAL NERVE GRAFT IN NEUROTROPHIC KERATOPATHY

INTRODUCTION

Neurotrophic keratopathy (NK) is a degenerative corneal condition that originates from damage to the trigeminal innervation and serves as an integral component of ocular surface homeostasis, blink reflex, corneal wound healing, tear production, and normal limbal stem cell function.[1,2] Sensory nerves secrete many neuropeptides, such as substance P, calcitonin gene-related peptide, and cholecystokinin, which are involved in trophic effects and their depletion induced by capsaicin, on culture in newborn mice evidenced neuroparalytic-like corneal alterations.[3] Neurotrophic keratopathy is the most intricate corneal condition that involves a stepwise therapeutic approach guided by the severity of the disease. All conventional measures are aimed at protecting the corneal surface and averting its epithelial breakdown.[4] Recombinant nerve growth factor (Cenegermin, Dompè Farmaceutici, Milan, Italy) emerges as much greeted advent in the management of NK and bestows a paradigm shift in medical management by addressing the root pathology.[5] However, its efficacy in clinical trials,[6,7] high costs, inability to address the underlying absence of corneal innervation and

subsequent perpetuation of progressive vision loss confine its widespread use in routine clinical practice. Therefore, Corneal neurotization (CN) has evolved as a potential therapeutic surgical technique, being able to re-establish the corneal sensation and reverse corneal alteration by providing a functional source of innervation.[8] This can be done directly by transposing the adjacent healthy nerve or indirectly by using nerve grafts coapted to the healthy donor nerve.[9,10] Both surgical techniques were attributed to the improvement in corneal sensations, notably 80% for direct and 83.3% success rate for indirect CN at one year.[11]

However, there are clinical questions to ponder, especially in the context of longer surgical duration, intricacies, multidisciplinary team involvement, and infrastructure facilities that preclude its frequent acceptance in routine practice. Hence, it provides a great impetus to appraise the outcomes of corneal neurotisation in therapeutically non-responding unilateral NK. Because of the heterogeneous etiology of NK in the recruited eyes, we preferred sural nerve graft coaptation to the contralateral supratrochlear nerve acting as a donor nerve to avoid the use of a possibly involved ipsilateral donor nerve.

METHODS

Study Design and Participants

A prospective interventional Corneal neurotization study using sural nerve graft coaptation to the contralateral supratrochlear nerve in 11 eyes of 11 patients with unilateral neurotrophic keratopathy, non-responding to the medical measures, during the period February 2021 to December 2021 was performed. The study conforms to the principles of the Helsinki Declaration and has received approval from the Institute Ethics Committee.

Neurotrophic keratopathy that was caused by viral keratitis, impairment of the trigeminal nerve following intracranial space-occupying lesions such as acoustic neuroma, damaged ophthalmic branch of the trigeminal nerve following neurosurgical events in patients with age more than 18 years and willingness to follow up were enrolled in the study. Eyes with associated lid malposition, prior corneal surgery, history of diabetes, leprosy or peripheral neuropathy and incomplete follow-up were excluded.

Demographic data comprises age, gender, the affected eye, diagnostic aetiology and duration of the disease recorded. Comprehensive ocular examination was performed in all the recruited eyes including best-corrected Snellen's visual acuity, slit lamp biomicroscopic examination of the ocular adnexa, anterior segment evaluation and posterior segment examination using +90Dioptre lens or B scan ultrasound in presence of media haze obscuring posterior segment visualization. Schirmer's 1 test[12] for tear production, fluorescein tear break-up time [TBUT][12] for tear film stability, National Eye Institute ocular surface staining scores[12] of cornea and conjunctiva describing ocular surface impairment and neurotrophic keratopathy grade determined by Mickie's classification[13] were recorded.

CORNEAL SENSATION MEASUREMENT

The central and peripheral (superior, inferior, nasal, and temporal) corneal sensation thresholds were evaluated using a Cochet Bonnet Aesthesiometer (CBA; Luneau, Paris, France) by direct contact, which stimulates the corneal nerves. The longest filament (6 cm; 0.12 mm diameter) corresponding to the lowest threshold was applied gently against the anterior corneal surface. Continual stimulation was provided by reducing the filament length in 0.5 mm steps until the stimulus was felt. The corneal sensation threshold

recorded was the measured filament length (cm), which provided a 50% positive response from four stimuli presentations.[14]

Central Corneal In Vivo Scanning Slit Confocal Microscopy Analysis

Confocal microscopy was performed in all eyes using the Heidelberg Retinal Tomograph with a Rostock corneal module (HRT3-RCM, Dossenhein, Germany). Central corneal images were obtained in manual gain mode using the standard setting of a 63X objective lens, utilizing a 670 nm red wavelength helium-neon diode laser as an illumination source. The three best images for each eye were selected for the analysis. Among the selected images, the best one, comprising the maximum number of nerves at the subbasal plexus level, was designated for analysis.

The subbasal nerve fiber layer was characterized by unmyelinated nerve fiber bundles consisting of straight and beaded fibers that course in the basal aspect of the basal epithelial cell layer on confocal microscopy. Sub basal nerve fiber length (SBNFL) image analysis was performed using freely downloadable ACC Metrics software (https://weillcornell.az1.qualtrics.com/jfe/form/SV_6o2ji0suM4jQinb).
ACC Metrics V.2 automatically analyzed the central confocal microscopy images with a field of view of 400×400 mm^2 obtained using the Heidelberg HRT III corneal confocal microscope and quantified the nerve fiber measurements, namely subbasal nerve fiber density (the total number of major nerves per millimeter squared of corneal tissue) and subbasal nerve fiber length (the total length of all nerve fibers and branches within the area of corneal tissue) from single or multiple corneal confocal microscopy images.

SURGICAL PROCEDURE

The sural nerve, acting as an interpositional graft, was used for corneal neurotization, as described by Elbaz et al.[9] in all recruited eyes with unilateral NK. A Multidisciplinary team of plastic surgeons (SG) and ophthalmologists (MS) performed the procedure (Fig 1). A longitudinal incision was made approximately 2 cm posterior and 2–3 cm proximal to the lateral malleolus to identify the sural nerve where significant branching of the nerve was not anticipated. The nerve was traced upward to obtain the desired length of 10–12 cm. Fascicles were separated by blunt dissection for a short distance at the distal end by creating a window in the epineurium, keeping the nerve under gentle traction and in the attached position itself. Fascicle separation before severing the sural nerve is infrequently performed. This facilitates smooth separation, mitigates possible collateral damage, and saves surgical time. The desired length of the sural nerve was cut at the proximal and distal ends and placed on a moist gauze piece.

At the same time, the supratrochlear nerve acting as the donor's nerve was accessed on the unaffected side using a transverse sub-brow incision extending at the level of the medial canthus to the medial limbus. The supratrochlear nerve passes beneath, and medial to, the supraorbital notch. It was accessed by tracing its branches to the confluence point, and the dissection was directed downwards at the periosteum and towards the medial canthus to expedite its consolidated identification and confirmed by neurovascular bundle visualization. Fascicle separation of the graft and consolidated identification of the donor supratrochlear nerve were the most time-consuming steps of the corneal neurotization procedure and were hastened by the above-mentioned practice.

The reversed sural nerve was then tunnelled over the nasal bridge to the affected side and coursed through a sub-brow incision into the superior conjunctival fornix onto the bulbar conjunctiva. The epineurium at the distal end of the sural nerve was separated under a microscope with fine dissection, and the separated fascicles were identified. Five segregated fascicles were secured using 10- nylon and fibrin glue at the limbus by passing through the subconjunctival space. End-to-side coaptation of the sural nerve graft with the donor supratrochlear nerve was achieved by creating an epineural window on the supratrochlear nerve and secured with fibrin glue and 10-0 nylon sutures. The skin was closed using interrupted 6-0 silk sutures. Postoperative topical steroid drops in the tapering dose, systemic and topical antibiotics, lubricating eye drops, and ointment were prescribed for 6 weeks with a therapeutic dose of antiviral drugs for six months for viral etiology NK.

FOLLOW-UP VISITS

The patients were followed-up at 1 week, 1 month, 3-month, 6-month, 9-month and 12-month. At each follow-up, best-corrected visual acuity, ocular surface evaluation [Tear film break up time (TBUT), Schirmer I test, and ocular surface staining score], central and four peripheral corneal sensations, and in vivo scanning slit confocal microscopy of the central cornea were repeated. The data were recorded by a blinded evaluator using a predesigned proforma.

STATISTICAL ANALYSIS

Quantitative variables are expressed as mean ± SD. The values obtained before and after the surgical intervention at different follow-ups were compared using the asymmetric significance 2-tailed test and Fisher's exact

test. Statistical significance was set at $p < 0.05$. The correlation between age/duration and corneal sensation/SBNF plexus was assessed using Spearman's rho coefficient with significance noted at the 0.01 level (2-tailed). SPSS version 20 program (SPSS Inc., Chicago, IL, US) was used for statistical analysis.

RESULTS

The demographic and clinical data of the 11 patients included in this study are shown in Table 1. The average duration of the underlying disease was 2.64±0.67 years (range, 2-4 years). There were six patients (54.54%) with NK stage II and five (45.5%) with NK stage III. All patients (100%) had completed a 6-month follow-up, 9/11(81.81%) had completed 9 months, and 6/11 (54.54%) had completed a 12-month follow-up visit following the procedure.

Ocular surface parameters showed significant improvement as early as 1 month, and over each follow-up visit in TBUT, Schirmer's 1 test, and corneal and conjunctival staining scores (Table 2) were associated with a significant reduction in NK grade. Healing of the ocular surface emulated a significant improvement in best corrected visual acuity from 1.35±0.52 (baseline) to 1.06±0.76 at 3 months (P=0.012). Significant improvement was observed at each sequential follow-up until the last visit (Table 2). Upon further analysis of the enrolled patients who completed 12 months of follow-up, two patients (33.33%) achieved 20/20 Snellen's visual acuity, as shown in Fig 2 and 3.

Improvement in corneal sensation was statistically significant in all quadrants compared to the preoperative value at follow-up visits until 1 year (P<0.05) (Table 3). It was demonstrated earliest in 8/11 (72.72%) patients at the 3-month follow-up and in 9/11 (81.81%) patients at the 6-month

follow-up. The two patients had completed a 6-month follow-up; however, no improvement was observed in corneal sensation.

Although in any of the recruited patients, sub basal nerve fiber density (SBNFD) could be calculated preoperatively, the baseline SBNFL was calculated to be 3.12±1.84. The values of SBNFL≤ 14.4mm/mm2 and SBNFD ≤ 14.7 no/mm2 were considered abnormal,[15] calculated using ACC Metrics V.2 software. Patients who had completed the 1-year follow-up showed a significant increase in SBNFD (P=0.028) and SBNFL (P=0.028). Moreover, the earliest significant improvement in SBNFD (P=0.018) was detected at the 6-month follow-up in of the 7/11 patients (63.63%). Nevertheless, the most significant increase in SBNFL (P= 0.00) was observed at the 1-month follow-up in 9/11 patients (81.81%) (Table 3). There was no association between the age of the patient and the duration of the disease with the recovery of corneal sensation and SBNFD (Table 4). No intraoperative or postoperative complications related to the surgical techniques were noted during follow-up.

However, two patients (one was of 27-year old with a history of nasal aspergillosis and the other one was 74-year-old with no systemic co-morbidity had reactivation of viral keratitis 3 and 6 months post-surgery, respectively. Systemic therapeutic doses of antiviral medications with topical steroids were instituted, and patients are being followed-up.

DISCUSSION

Corneal neurotisation has evolved as an effective option in the treatment of neurotrophic keratopathy. However, these techniques are not free of predicaments. Our study observed that consolidated donor nerve identification and interpositional nerve graft fascicle separation without

collateral damage were the most time-consuming and imperative steps in determining the success of corneal neurotization. Knowledge of anatomical variation and landmarks of donor supratrochlear nerve and sural nerve fascicle separation in the taut position before severing with the use of fibrin glue to secure fascicles around the limbus, perhaps measures to emulate and expedite the surgical procedure. Hence, we attempted these surgical variations in 11 recruited eyes with non-responding neurotrophic keratopathy and evaluated the long-term clinical outcome of the burgeoning corneal neurotization procedure.

In our study, a gradual resolution of corneal clouding with a corresponding improvement in visual acuity was observed as early as three months (P=0.012) that continued until the last follow-up 1-year (P=0.027). However, no general acquiescence to vision improvement has been reported in the literature following corneal neurotization. Leyngold *et al*[16] reported noteworthy vision improvement from 20/70 to 20/20 in one operated case, whereas Jowett and Pineda[17] noticed modest vision improvement in their reported series. In contrast, Benkhatar and colleagues found no improvement in vision.[18] This incongruity can be attributed to variations in the surgical methodology used by different authors, patient selection, disease duration, structural integrity of the cornea, and pre-existing corneal scarring.[9]

At 1-month follow-up, a statistically significant improvement in ocular surface parameters [TBUT (P=0.035), Schirmer's 1 test (P=0.005), corneal staining scores (P=0.016), and conjunctival staining scores (P=0.011)] was noted before visual improvement was observed. Amelioration in ocular surface parameters, predominantly corneal staining score improvement, is pertinent to NK grade improvement, hence explaining the concordant

improvement in NK grades at the 1-month clinical examination. Substantial recovery of the ocular surface is closely linked to corneal sensation restoration. Studies have shown that corneal innervation plays a pivotal role in the proliferation of corneal epithelial or limbal stem cells after injury.[2] This is supported by evidence that interactions between the corneal epithelium and corneal innervation upregulate the expression of a5 integrins and E-cadherin, which are necessary for epithelial adhesion to fibronectin in the extracellular matrix and to maintain the integrity of the corneal epithelium.[19]

In our study, corneal sensation improvement at a statistically significant level was noted at 3 months postoperatively (11/11eyes), consistent with Elbaz et al.,[9] Malhotra R et al[20] annotations. Improvements continued for a year after the procedure; however, a longer time course has been reported in earlier studies.[21] A similar observation of corneal sensation improvement at a 3-month follow-up with maximal sensation at 6 months was reported by Kim et al[22] in herpetic NK. However, previous studies [4,18,21] and the recently published Rathi et al[23] interim reports observed objective improvement in corneal sensation at 5–6 months. The return of corneal sensation [central (P=0.029), superior (P=0.007), inferior (P=0.009), nasal (P=0.009), and temporal (P=0.007]) was significant in our study, although the absolute value to the contralateral normal cornea was not attained (Fig 4), which is consistent with the results of previous studies.[4,18]

Anatomical evidence of corneal reinnervation on in vivo confocal microscopy is a protracted process that begins with augmentation of corneal subbasal nerve fiber length, detected as early as the 1-month follow-up. Subsequently, the subbasal nerve fiber density became apparent on in vivo confocal microscopy at the 6-month follow-up and progressively increased;

however, a linear improvement curve was not established (Fig 5). Our study observed the outcomes harmonized with the findings of Benkhatar et al., confocal microscopic subbasal nerve plexus improvement commenced as early as 3 months, with progressive increment over 3–6 months before stabilizing.[18] Our study documented a significant improvement in the subbasal nerve plexus for a year [SBNFD (P=0.025), SBNFL (P=0.00)].

Our study speculates an initial increase in sub-basal nerve fiber length, connoting escalation of pre-existing sub-basal nerves and subsequent generation of new nerve bundles over six months and continued at one year (Fig 6). Interestingly, these budding nerve terminals were arranged chaotically and did not follow this pattern. Thus, our study reported that the chronological order of the corneal reinnervation process commenced with an escalation of pre-existing SBNFL spans from 1-month post-surgery, followed by the objective perception of corneal sensation, which spans from 3-month and improvement in SBNFD from 6-month to 1-year following corneal neurotization. The exact mechanism of corneal reinnervation following neurotization is yet to be understood completely because the distal donor nerve fascicles are laid around the limbus and not directly coapted to the remaining corneal nerves. By coaptation of the supratrochlear nerve, the new basal laminae of Schwann cells in the donor nerve graft support axonal regeneration that finds their way from the surrounding nerve graft fascicles to the corneal stroma or at least to the subepithelial level, thereby restoring sensation.[9]

Despite the promising results of corneal neurotization, two patients with herpes simplex neurotrophic keratopathy developed recurrence in our study. Twenty-seven-year-old male with an antecedent history of paranasal sinus Aspergillus infection developed disciform stromal keratitis at 6-month

post-surgery, whereas, a seventy-four-year-old male without systemic illness reported a central epithelial defect three months after the procedure. A review of the literature on the reactivation of herpes simplex keratitis revealed that, in addition to cytokines and chemokines, neuropeptide-substance-P, glycoproteins, microRNAs, and other mediators contribute to the pathological immune response of herpes simplex keratitis. All these regulators play dual roles in inhibiting and promoting disease pathogenesis.[24] Therefore, reactivation of the latent virus in the context of hypoimmunity (common in both recurrent patients) during the escalation of the sub-basal nerve plexus and consequent release of neuropeptides resulted in recurrence. However, cellular immunity, inflammatory factors, and molecular assays would help clarify the immunopathological process of reactivation following neurotisation. Both patients continued a therapeutic dose of systemic antiviral medication with topical antibiotic ointment. Topical steroids were also added to the disciform stromal keratitis, and marked improvement in vision from 20/80 to 20/40 with resolution in stromal keratitis was observed 5-months after initiation of the treatment; however, older patients showed no recurrence in vision with resolution of the epithelial defect at 7-months.

In the literature, young patients have been associated with faster and more complete recovery.[25] However, no discernible correlation was noted between age and improvement in corneal sensation and subbasal nerve plexus parameters. Similarly, a large sample size would have helped establish a correlation between SBNFD and disease duration. Complications at the donor site related to sural nerve graft harvesting, such as loss of sensation, discomfort, and allodynia in the lower leg or foot[26] were anticipated; however, none of these complications were observed at three months postoperative.

CONCLUSION

In summary, our study demonstrated the efficacy of corneal neurotization in treating the underlying pathology of neurotrophic keratopathy and substantiated the routine practice of this technique by simplifying the intricacies observed during the procedure.

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

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AUTHOR CONTRIBUTION STATEMENT

MS, AK, SG were responsible for designing and conducting the study and writing the manuscript. **CM, AG, TS, KS** were responsible for data acquisition, analysis, and interpretation of the study results. **PCG, MSi** contributed to data acquisition, drafting, and critical revision of intellectual input. **AKJ** holds overall responsibility for the accuracy and integrity of the work and contributed to the conception and design of the manuscript, critical revision, and final approval of the manuscript for publication.

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Table 1 Demographic characteristics of the eyes with neurotrophic keratopathy, underwent corneal neurotization using sural nerve graft in the study

Demographic data	Neurotrophic keratopathy Eyes
No of eyes	11
Gender (M/F)	7/4 (63.6%/36.4%)
Age mean±SD, (range)	44.55±21.38, (25-74years)
Affected eye	
Right eye	8 (72.7%)
Left eye	3 (27.3%)
Diagnosis	
HSV	6 (54.5%)
HZO	1 (9.1%)
Facial nerve palsy	4 (36.4%)
NK grade	
Grade 1	0
Grade 2	6 (54.54%)
Grade 3	5 (45.5%)
Duration of aetiology mean±SD, (range)	2.64±0.67, (2-4 years)

Data are presented as no. (%) or mean ± standard deviation unless Otherwise indicated

Table 2 Result of ocular surface evaluation tests (mean±SD) following corneal neurotization using sural nerve graft in eyes with neurotrophic keratopathy

Outcomes	No of eyes	BCVA	TBUT (s)	Schirmer's 1 test (mm)	Cornea staining scores	Conjunctival staining scores	NK grade
Pre-operative	11	1.35±0.52	3.00±1.94	5.45±3.35	8.18±2.44	6.64±2.54	2.45±0.522
Post-operative							
1-mont	11	1.22±0.68	4.55±2.42	7.36±3.72	7.18±2.99	5.09±2.21	2.36±0.50
3-month	11	1.06±0.76	5.36±2.42	8.27±3.69	3.73±2.00	2.18±1.16	1.64±0.80
6-month	11	1.03±0.76	6.18±2.71	9.00±3.46	1.91±1.37	0.91±0.70	1.64±0.92
9-month	9	0.94±0.76	7.44±2.65	10.11±3.72	1.33±1.32	0.67±0.50	1.44±0.52
1year	6	0.55±0.60	9.50±2.81	12.83±3.92	0.50±0.54	0.33±0.51	1.00±0.63
P-value		0.03	0.001	0.001	0.001	0.001	-
Pre vs 1-month		0.17	0.007	0.017	0.016	0.011	0.015
Pre vs 3-month		0.012	0.012	0.016	0.003	0.003	0.113
Pre vs 6-month		0.012	0.005	0.005	0.003	0.003	0.015

Pre vs 9-month	0.017	0.007	0.012	0.008	0.007	0.008
Pre vs 1 year	0.027	0.027	0.027	0.026	0.027	0.333

Table 3 Clinical outcome of corneal neurotization on central and peripheral corneal sensation and central corneal sub-basal nerve fibre plexus in eyes with neurotrophic keratopathy

Outcomes	No of eyes	CORNEAL SENSATIONS					SBNFD no/mm^2	SBNFL mm/mm^2
		Central	Superior	Inferior	Nasal	Temporal		
Pre-operative	11	0.045±0.15	0.045±0.15	0.091±0.20	0.045±0.15	0.045±0.15	0.00±0.00	3.12±1.84
Post-operative								
1-month	11	0.045±0.15	0.045±0.15	0.091±0.20	0.091±0.20	0.045±0.15	0.00±0.00	4.49±1.88
3-month	11	0.59±0.86	0.63±0.83	0.81±1.12	0.81±1.14	0.95±1.31	0.58±1.64	6.26±2.58
6-month	11	1.09±1.48	1.54±1.54	1.50±1.56	1.50±1.48	1.72±1.61	1.83±2.54	7.82±3.29
9-month	9	1.33±1.58	1.94±1.62	1.94±1.62	1.88±1.70	2.11±1.85	2.59±2.92	9.41±3.13
1-year	6	1.25±1.57	3.16±1.66	3.33±1.80	3.41±1.65	3.41±1.65	4.90±3.12	13.31±3.61
P-value		0.029	0.007	0.009	0.009	0.007	0.025	0.000
Pre vs 1-month		1.00	1.00	1.00	0.56	1.00	1.00	0.008
Pre vs 3-month		0.024	0.014	0.026	0.016	0.016	0.180	0.003
Pre vs 6-month		0.018	0.011	0.011	0.007	0.007	0.018	0.003

Pre vs 9-month	0.017	0.011	0.011	0.011	0.011	0.028	0.008
Pre vs 1 year	0.027	0.027	0.027	0.027	0.027	0.028	0.028

Table 4 Correlation of age and duration with central corneal sensation and sub basal nerve fiber density (SBNFD) at follow up visits

Correlation	Central corneal sensation (correlation coefficient)	P-value	SBNFD (correlation coefficient)	P-value
Age				
6-month	0.057	0.86	0.072	0.833
1-year	0.00	1.00	-0.086	0.872
Disease Duration				
6-month	0.32	0.32	0.216	0.523
1-year	-0.016	0.976	-0.185	0.725

*correlation is significant at the 0.001 level (2-tailed)

This paper was judged as the BEST PAPER of Cornea – II Session

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LVPEI

SELECTIVE ENDOTHELIALECTOMY IN PETERS ANOMALY (SEPA): A PROSPECTIVE CLINICAL TRIAL

ABSTRACT

Purpose: This study describes the surgical outcomes of selective endothelialectomy in Peters anomaly (SEPA), a relatively new technique to manage Peters anomaly (PA).

Methods: This study included 50 eyes of 40 children who had a visually significant posterior corneal defect due to PA and underwent SEPA between 2019 and 2022. A selective endothelialectomy from the posterior corneal defect was performed while preserving Descemet's membrane. The primary outcome measure was the resolution of corneal opacification. The secondary outcome measures were functional vision, complications, and risk factors for failure.

Results: At a mean postoperative follow-up of 0.8 ± 1.46 years, All the eyes maintained a successful outcome. Mean pre-and post-operative best-corrected visual acuity were 2.41 ± 0.21 and 1.85 ± 0.14 (p=0.002), respectively. Ambulatory functional visual improvement was seen in 35%, 62.2% attained vision ranging between 20/800 to 20/200 and 2.7% attained vision ranging between 20/190 and 20/50. Risk factors for the

failure to clearing the corneal opacity was age at surgery. There were no sight-threatening complications.

Conclusion: SEPA is a safe and effective technique in select cases of posterior corneal defect due to PA. SEPA could be a potential surgical alternative to pediatric keratoplasty and or optical iridectomy in children with a visually significant central corneal opacification due to PA.

INTRODUCTION

Peters anomaly (PA) is the most common indication for penetrating keratoplasty (PK) among congenital corneal opacities.[1] PA is a developmental abnormality in which the corneal defect is mostly limited to the cornea's posterior layers and, if untreated, can result in sensory deprivation amblyopia.[1] Step ladder clinical categorization based on a constellation of clinical signs includes Type 1 disease depicted by central corneal opacity with peripheral iridocorneal adhesions extending from the iris collarette to the perimeter of the corneal opacity (Figure 1a), and Type-2 disease featuring kerato-lenticular adhesions, which may result in a rudimentary, fragmented, or partially resorbed lens (Figure 1b).[2-4] In Peters plus anomaly, bilateral peninsular-like corneal opacification in the posterior stroma and corresponding defects in Descemet's membrane (DM)-endothelium complex are noticed besides typical systemic features.[5-7] Bilateral disease is seen in 80% of PA,[5,] and type-2 disease is more often associated with poor visual outcomes than type-1 disease.[2,5,8-14] Anterior segment optical coherence tomography (AS-OCT) observation has shown a double-layered DM in PA,[15] explaining a reason for spontaneous non-healing of these defects. Histopathology of PA shows focal abnormal posterior corneal stromal architecture with an absence of DM (Figure 1d) and markedly attenuated endothelium with uveal pigment deposits around the

defect's edges.[16,17]

In the last two decades, the understanding of corneal endothelial cell biology and endothelial transplantation techniques have evolved considerably. For instance, when the peripheral endothelium is healthy, corneal endothelial defects heal rapidly following an injury or insult. However, in PA, where the central corneal endothelium is abnormal and might inhibit centripetal expansion and normal healing, the normal corneal endothelial physiologic features are disrupted, resulting in persistent corneal edema and opacification.[18] This inhibition of centripetal expansion in PA and its consequences, i.e., corneal edema and opacity, can be significant causes of corneal blindness.[1] Recent literature supports the idea that the peripheral corneal endothelium is capable of self-renewing after a Descemetorhexis in Fuch's endothelial dystrophy.[19] Management options include a conservative approach in mild central corneal opacification, along with mydriatics and occlusion therapy.[20] PA with more extensive central opacities can be surgically managed with a variable success rate. Optical iridectomies,[20] rotational keratoplasty,[21] conventional full-thickness keratoplasty,[2,8,9,11,12,22,] and primary keratoprosthesis are the various surgical options used in severe cases.

In the past, visually significant PA was treated with penetrating keratoplasty (PK), where the outcomes are highly variable and often suboptimal in the long term. Graft failure rates have been reported to be 50%-100% at ten years,[2] and there is a high incidence of post-operative complications such as allograft rejection, suture-related issues, wound dehiscence, and secondary glaucoma that further compromise the long-term outcomes.[2,8,11] Therefore, the surgeon's preference rather than scientific evidence usually determined the technique to be adopted.

Having performed more than 200 full-thickness corneal transplantations in PA with variable results, we chose to adopt selective endothelialectomy in Peters anomaly (SEPA), a novel technique for treating corneal opacification in PA in the year 2012. This technique showed that the selective removal of abnormal corneal endothelial cells underlying the posterior defect could reverse corneal edema and corneal scar remodeling, eliminating the need for full-thickness keratoplasty. Our initial unplanned experience of spontaneous regression of corneal opacification in kerato-lenticular dysgenesis following lens removal with endothelial scraping had prompted us to critically review our previous cases that had undergone synechiolysis with endothelialectomy. Also, we found an anomalous layer over the PA consistently, which was corroborated on AS-OCT (Figure 1c) and histopathology (Figures 1d-f). Similarly, two independent authors have published successful outcomes by selective endothelial removal (SER) and Descemetorhexis.[23,24] Previously we have demonstrated successful outcomes in our retrospective study by performing Selective Endothelialectomy in Peters anomaly (SEPA), removing abnormal corneal endothelial cells underlying the posterior defect could reverse corneal edema and facilitate corneal scar remodeling, thus eliminating the need for full-thickness keratoplasty. However, the results needed validation in a prospective study involving a large sample with a longer follow-up for broader acceptance of the SEPA technique. Therefore, we report the prospective surgical outcomes of SEPA in a large cohort of children with PA.

Materials and Methods

The Institutional Ethics Committee of L V Prasad Eye Institute, Hyderabad, India, approved the study. This study was conducted in strict adherence to the tenets of the Declaration of Helsinki. All legal guardians of children who underwent SEPA and additional interventions (optical iridectomy or

endocapsular lens aspiration with limited anterior vitrectomy) gave informed written consent for all procedures described in this study. This was a prospective, non-consecutive, interventional clinical case series. A total of 50 eyes of 40 children with non-resolving corneal edema, diagnosed with Peters Anomaly at L V Prasad Eye Institute, Hyderabad, India, between 2019 and 2022 that underwent SEPA were included. The affected eyes of children with a PA were evaluated for size and density of the posterior corneal opacity, improvement in visual functions, and AS-OCT of the posterior corneal defect performed before and after surgery in cooperative children.

Grading of disease severity: We classified the disease severity and zonal involvement as defined previously by Yang et al.[2] Clinically, PA is classified based on the constellation of clinical signs. As described in the authors previously published study.

Zone of corneal opacity: The location and extent of the opacity were ascertained based on digital photos, surgical videos, drawings, and other descriptive information in the medical records. The location of the opacity was described in three zones centered on the geographic center of the cornea. Zone 1 (central cornea) was circular with a diameter of 5 mm. Zone 2 (peripheral cornea) extended from zone 1 up to the limbus.[2]

Designation of laterality: Eyes of patients with visually significant involvement of both eyes were designated as having significant bilateral disease. Eyes of patients with unilateral disease or asymmetrical bilateral disease in which the corneal opacity in the lesser affected eye was minimal, extra-axial, and visually insignificant were designated as having unilateral disease.

All children who underwent SEPA met the following inclusion criteria: children with a type 1 or 2 Peters anomaly with a posterior corneal defect limited to zone 2 and affecting the visual functions and precluding the retinoscopy or fundus view under undilated circumstances were considered for SEPA. The cases excluded were eyes with pan corneal involvement, Zone 3 corneal opacity, those with staphyloma, secondary glaucoma, microphthalmia, persistent fetal vasculature, aniridia, and those unwilling to undergo a conservative surgical intervention. Pre-operative vision testing, corneal pachymetry, and AS-OCT were performed in all the cooperative children. Parents consented with emphasis that this was a conservative surgical intervention that did not need a long-term stringent follow-up and medications and that there was no risk of graft failure. All parents understood that this innovative surgical intervention might have a modest outcome, and definitive intervention like full-thickness corneal grafting might be necessary in the future. Alternative options including optical iridectomy, rotational autograft, and additional lens removal with concurrent or subsequent PK were discussed with the parents.

Surgical technique of SEPA: As described in the authors previously published study.

Additional interventions: Lysis of visible delicate iris strands was performed when noted to arise from the iris collarette and extend to the perimeter of corneal opacity. **SEPAO**: Optical iridectomy or sphincterotomy was done where the corneal opacity was > 6 mm or seen obscuring the retinal red reflex without dilation. Optical iridectomy (size of at least three clock hours) was performed using a vitrector and aimed to achieve a decent red reflex intraoperatively. **SEPAL**: Lens aspiration (LA) along with primary posterior capsulotomy (PPC) and a limited anterior vitrectomy (AV) was

considered when the lens was adherent to the posterior corneal surface. All ports were closed using 10-0 nylon sutures. Following the procedure, a drop of topical moxifloxacin 0.5% eye drops (Alcon Labs, Fort Worth, Texas, USA), prednisolone acetate 1% eye drops (Alcon Labs, Fort Worth, Texas, USA), and atropine sulphate 1% eye drops (Aurolab, Madurai, India) were instilled.

Postoperative and follow-up schedule: As described in the authors previously published study.

Optical coherence tomography scan (AS-OCT): AS-OCT imaging was performed before the intervention either using handheld spectral-domain optical coherence tomography (Bioptigen, Inc., Research Triangle Park, NC) under general anesthesia or preoperatively using RTVue-100 FD-OCT (Optovue, Fremont, California) OCT in the office setting in cooperative children. The evaluated parameters included the zone of the extent of corneal opacity, iridocorneal or corneo-lenticular adhesions, and anterior chamber depth.

Data collection: Data collected included patient age, gender, laterality, detailed pedigree, details of prior eye surgeries, if any, duration of corneal opacification, pre-operative visual acuity and IOP, intra-operative surgical details, post-operative complications, length of follow-up, and status of DM, IOP and optic nerve head health at each visit. Visual acuity was measured using age-appropriate grating acuity in infants and Teller Acuity Cards in young children or linear Sloan letters in older children. Blink or grimace to light was defined as light perception. Centered/steady/maintain or fix and follow were defined as hand motion. Visual acuity values were converted to the logarithm of the minimum angle of resolution (log MAR) equivalence. The significant post-operative primary outcome measures included corneal clarity (cleared, partly cleared, and not cleared). The secondary outcome

measures included best-corrected visual acuity (BCVA). The impact of laterality, pre-operative age at surgery, size of opacity, additional intervention, and postoperative factors on the clinical resolution of corneal opacification was analyzed.

Outcome measures of efficacy: The primary outcome measure was the clinically significant resolution of corneal opacification after SEPA. Successful resolution of corneal opacification was defined as a partial to near-total stromal clearing without epithelial or stromal edema allowing a clear view of iris features, retinoscopy, and fundus evaluation. Successful SEPA was also described as a reduction in corneal opacification's size and density at the last follow-up without a later surgical procedure. Failure was defined as a posterior corneal opacification failing to show clinical resolution even after three months following SEPA, precluding the visibility of iris details, retinoscopy, or retinal examination, and a need for additional intervention for visual rehabilitation. The secondary outcome measure of efficacy was the improvement change in BCVA at each postoperative follow-up visit.

Cases were categorized based on a clinical resolution of corneal edema and scar remodeling: cleared, partly cleared. Cleared was considered when there was a complete resolution of corneal edema with a discernible scar remodeling by 3 months that allowed a decent retinoscopy reading in undilated condition. Partly cleared had a significant clearing but needed pupillary dilation for a decent retinoscopy reading by the post-operative month three visit.

STATISTICAL ANALYSIS:

The statistical analysis was performed using STATA v14.2 (Stata Corp, College Station, TX, USA). The distribution of continuous data was tested for normality using the Shapiro-Wilk test. Continuous, normally distributed variables were represented as mean ± standard deviation. Median and inter-quartile range (IQR) were used to describe continuous non-parametric data. Categorical data were expressed in proportions. A mixed-effects model with a random intercept at the subject level was used to account for the correlation between the fellow eyes of the same patients in the comparison of data between visits and in the analysis of risk factors for failure. Also, the outcome data were compared among the types of surgical intervention: SEPA alone with/without synechiolysis, SEPAO, and SEPAL. A p-value of <0.05 was considered statistically significant.

RESULTS

During the study period (2019-2022), a total of 50 eyes of 40 children diagnosed with posterior corneal opacity due to PA underwent SEPA with or without additional procedures (optical iridectomy or endocapsular lens aspiration with limited anterior vitrectomy). 37 eyes of 27 children having at least 6 months of post-operative follow-up were included for the analysis Seventeen children (60.7%) were males. Parental consanguinity was noted in 7/36 children (19.4%). Twenty-six eyes (70.3%) of 16 children are with a visually significant bilateral disease, while 11 eyes of 11 children (29.7%) had unilateral involvement.

Table 1 summarizes the baseline demographics by the type of procedure performed. Mean age at presentation, gender, zone of involvement of the opacity were comparable among the three interventions SEPA, SEPAO, and SEPAL. Whereas laterality, and consanguinity were not comparable among three interventions. All eyes with Type 2 PA underwent SEPAL.

The mean age at the time of SEPA was 0.8 ± 1.46 years. Seven eyes (19%) were in children who were older than 12 months of age at first intervention. The post-interventional mean follow-up period was 1.27 ± 0.67 years. Table 2 summarizes the outcomes by the type of procedure performed.

EFFICACY OF SELECTIVE ENDOTHELIALECTOMY:

Cleared: Among 37 eyes, 21 eyes (56.8%) had a significant clearing of the corneal opacification. These eyes maintained a clear optical axis with a gradual reduction in the density of corneal haze, which was evident three months post-intervention, besides expansion of overall corneal diameter, and no further re-intervention was necessitated. The proportion of eyes with cleared cornea were not comparable among the three intervention groups (Table 2).

Partly cleared: 16 eyes (43.2%) eyes had a discernible change in corneal clarity and an acceptable functional vision. Detailed refraction was possible on complete dilation or through an iridectomy opening. In this subset post-operatively, we did not observe any glare or photophobia. The proportion of eyes with partly cleared cornea were also not comparable among the three intervention groups (Table 2).

Post-operative visual function: Among 37 eyes at presentation, only three eyes (8%) had vision better than 20/800, 13 (35.1%) had an ambulatory vision and 21 (56.8%) had non-ambulatory vision. Post-intervention, 13 (35.1%) eyes had ambulatory vision, 23 (62.2%) eyes had vision between 20/800 to 20/200, and one (2.7%) achieved a BCVA of 20/190 or better at the final follow-up. In cleared corneas, there was significant improvement in visual acuity when compared with partly cleared corneas (1.75 ± 0.14 vs 2.0 ± 0.15, p=0.02). Whereas visual outcomes were comparable among three

surgical interventions (p=0.57). Suboptimal visual improvement was due to dense amblyopia. The mean spherical equivalent refraction (MSER) at the final visit was 3.35 ± 6.63 D. (Table 3). The MSER was not comparable among cleared corneas vs partly cleared cornea (1.98 ± 1.45 vs 4.92 ± 1.48, p= 0.003) and among the surgical interventions, SEPA vs SEPO vs SEPAL (0.26 ± 1.77 vs 1.61 ± 1.12 vs 14.8 ± 2.4, p<0.0001).

Safety of SEPA in the operated eye: None of the eyes that received SEPA and its one of iterations had a DM detachment, persistent corneal edema, lens touch or uveal trauma. The most common observation in the operated eye was corneal edema at the site of SEPA intervention. The corneal edema resolved spontaneously within one month postoperatively, as demonstrated in AS-OCT analysis (Figures). AS-OCT confirmation was available in 56.8% (21) eyes. There were no sight-threatening complications documented. None of the eyes had a decline in visual functions post-operatively.

Anterior segment optical coherence tomography (AS-OCT) analysis: AS-OCT images of pre-and post-intervention were available in 21 eyes (57%) for detailed scrutiny. Analyzed images revealed that the Bowman's membrane over the corneal defect appeared either disrupted or absent, while the rest of the anterior stromal architecture was comparatively preserved. Overlying the DM defect, the posterior stroma had a denser reflectivity with varying stromal thinning and excavation. The edges of defects were thickened and rolled out, and few cases showed a presence of anomalous pre-Descemet's layer occupying the posterior concavity. There were numerous, delicate iris strands extending between the iris collarette and edges of the corneal defect in most cases. In an example, of type-1 Peters anomaly with a posterior corneal opacification with uveal pigment dispersion pre-operatively and post-SEPAO showed a significant clearing of opacity and sharp reflectivity

pattern on AS-OCT suggestive of DM covering the defect. Figure: Zone-2 PA Image captured 1-month post-SEPA (A) with a significant opacification was followed sequentially, and cornea cleared in 12 months (B) same corroborated on AS-OCT (C). D: Zone-1 type-1 PA with central excavation corresponding to AS-OCT image (F) showed a marked improvement at the post-op visit of 2.5 years. In summary, AS-OCT analysis suggested healing pattern after SEPA over the original site of posterior excavation.

Resolution of opacity after SEPA: Table 4 shows comparisons between SEPA, cleared cornea and partly cleared cornea groups. In bivariate analysis, only age at surgery is significant risk factors for the failure to clearing the corneal opacity.

DISCUSSION

Our study validates the outcomes of SEPA, a novel and less invasive surgical strategy for the treatment of children with PA and provides surgical outcomes in a cohort. SEPA is based on the following assumptions in PA: (1) focal area of anomalous DM-endothelial complex underlying posterior corneal defect, (2) peri-lesional healthy endothelium has regenerative potential to fill in the denuded area, (3) robust scar remodeling in children, and (4) relatively well preserved overlying anterior stromal architecture.[17] The anomalous endothelium inhibits normal expansion of the surrounding peripheral corneal endothelium, leading to localized loss of endothelial pump function and corneal edema.[18] Therefore, it is logical to believe that there could be an improvement if the abnormal endothelium is removed, resulting in defects being replaced with healthy peri-lesional corneal endothelium. More recently, the corneal endothelial wound models have demonstrated that following a localized corneal endothelial removal, neighboring cells will enlarge and migrate to restore the anatomical and

functional integrity of the corneal endothelial monolayer.[19,25,26] Based on these findings, we believe that SEPA, while preserving the DM, and might promote spontaneous endothelial migration, thus simply accelerating the spontaneous resolution of corneal edema and opacification, consequently evading limitations PK in children with PA.

While PA is the most common indication of corneal transplantation among childhood corneal blindness,[10] it is challenging to visually rehabilitate these children, considering the complexity of corneal and anterior segment involvement.[2,22,27,28] PA type-2 variant often requires sequential lens-based intervention followed by PK.[29] Associated comorbidities necessitate further intervention that in turn compromises the long-term graft survival.[9] PA type-1 cases typically fare better than PA type-2.[2] The visual and functional prognoses in both groups of patients are modest.[2] Furthermore, there are several intra-operative challenges and post-operative complications that limit the long-term prospects of PK.[2,8] The alternatives to PK include pharmacological dilation, rotational corneal grafts, optical sector iridectomy, and spontaneous resolution, which have had different success rates.[20,21,30]

The technique of the approach in each case was governed by the disease severity, associated comorbidities, child's visual potential, parents' expectations, and surgeon's preference. Several studies give importance to the anatomic and surgical results, and a small subset focuses exclusively on long-term functional outcomes of PK in children with PA. Supplementary digital content 3 provides an overall comparison of this study's results with that of other large series consisting of different surgical interventions for PA.[2,8,10-12,14,20,31-34] We realized that PK had an inferior long-term outcome and merited stringent follow-up and had the risk of graft infection, allograft rejection, secondary glaucoma, suture-related issues, astigmatism, graft-host

dehiscence, and reintervention if graft fails.[11] Because the inclusion criteria and definition of success vary across studies; superficial comparisons sometimes can lead to deeply flawed inferences. Therefore, it may be worthwhile to limit the comparison with our own experience of PK in PA. Our historical results agree with previous studies with an overall modest success rate of 21% at the end of 2 years in children with PA,[11] and similar results were mirrored in a recent study published by Sun et al.[14]

A larger zonal involvement of 4 to 6 mm requires more than double the surface area for the remaining endothelium to repopulate (4π vs. 9π).[19] In contrast, an 8 mm defect may require a repopulation of 4 times that of the area of a 4 mm of endothelial scraping.[19] Therefore, the ideal case selection for this new technique is mild to moderate PA cases with smaller zonal involvement than 7 mm. Although most eyes with successful outcomes showed a marked reduction in corneal edema within one month of SEPA, the central corneal haze showed a gradual decline ranging from 6 to 18 months. This suggests that eyes with denser opacity within the surgical cohort showed the considerable time for stromal clearing and scar remodeling.

Outcomes after SEPA are dependent on undisturbed anterior stromal architecture, an island of the transparent cornea in the center or mid-peripheral region, and healthy peripheral corneal endothelial cells. Endothelial migration requires breakage of contact inhibition of anomalous endothelial cells; hence, adhesiolysis alone would not have allowed cell migration of healthy cells and restoration of endothelial pump function with a lessening in stromal opacity. While mild-moderate cases where opacity was limited to zone-1 tend to have excellent outcomes, severe cases limited to zone 1 or 2 may fare better if concurrent endocapsular lens aspiration with optical iridectomy is considered along with SEPA. Primary PK can be

deliberated in cases with extensive corneal involvement (Zone 3B), corneal ectasias, or staphyloma formation after a perforation. Besides more extensive cornea involvement, the visual impairment in PA is frequently due to associated comorbidities; hence, while selective endothelialectomy may improve corneal transparency, the overall visual prognosis may remain poor without other interventions like prompt amblyopia therapy and glaucoma control.

This study also sheds new light on the possible factors responsible for the failure of SEPA. The analysis revealed that the severe disease, presence of microcornea, high IOP, concomitant lens aspiration with vitrectomy, and female gender were identified risk factors for non-clearing after SEPA. Inadvertent DM detachment at the time of SEPA should be avoided because it necessitates additional intervention, which in turn, adversely impacts SEPA outcome. Therefore, it may be advisable to preemptively identify those eyes with wider corneal involvement, corneo-lenticular attachment, ectasia, extremely thin cornea, perforation, and a staphyloma formation by performing an OCT or ultrasound biomicroscopy before surgery.[16,36]

The study's major strengths are the sample size, single-center design with experienced pediatric corneal surgeons, and long follow-up. Five independent masked evaluators validated the diagnosis, and outcomes were assessed in every case. Other more objective means such as AS-OCT or image analysis of post-operative outcomes could have been used. However, considering that 3/4th of the cohort constituted young children, it would have meant additional anesthesia examination at each follow-up visit to perform AS-OCT or capture images, and these were not feasible. The lack of events (non-clearing) among Type 1 PA suggests that the results may not be generalized to represent the entire cohort of SEPA.

The findings of this study question the paradigm whether this procedure should be offered as a preferred surgical modality in all children with PA or only in select cases, where PK is not the preferred alternative, such as in areas where there is a scarcity of donor tissues, non-compliance, inability to follow-up or high-risk cases. We have demonstrated, to the best of our knowledge for the first time that, the SEPAL technique can be used even in cases of kerato-lenticular adhesion as long as the opacity is not greater than 6 mm or at least half of the peripheral cornea is clear. We have shown that, by being used in the manner described by us, SEPA may circumvent these limitations drawing from our favorable experience in infants and children with PA. This study showed that SEPA results are extremely promising, and SEPA can be an effective surgical alternative to optical iridectomy and full-thickness PK benefitting hundreds of children with PA-related blindness worldwide.

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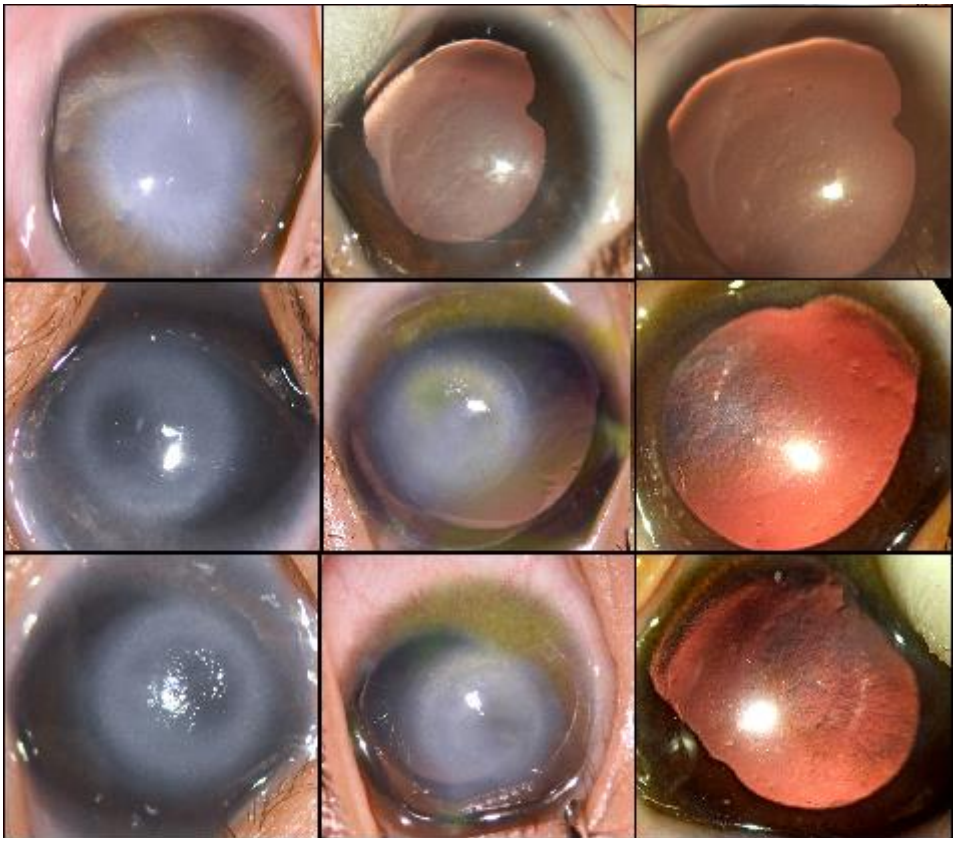

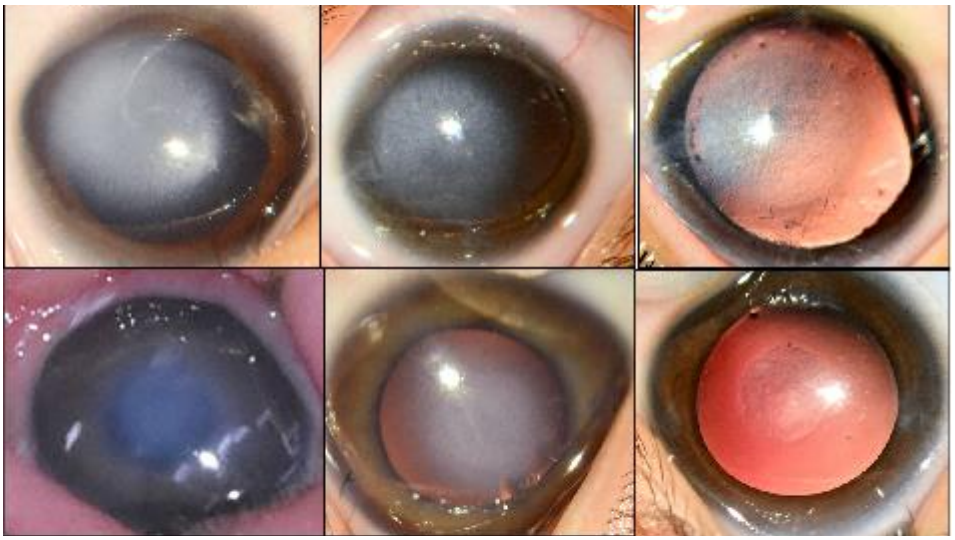

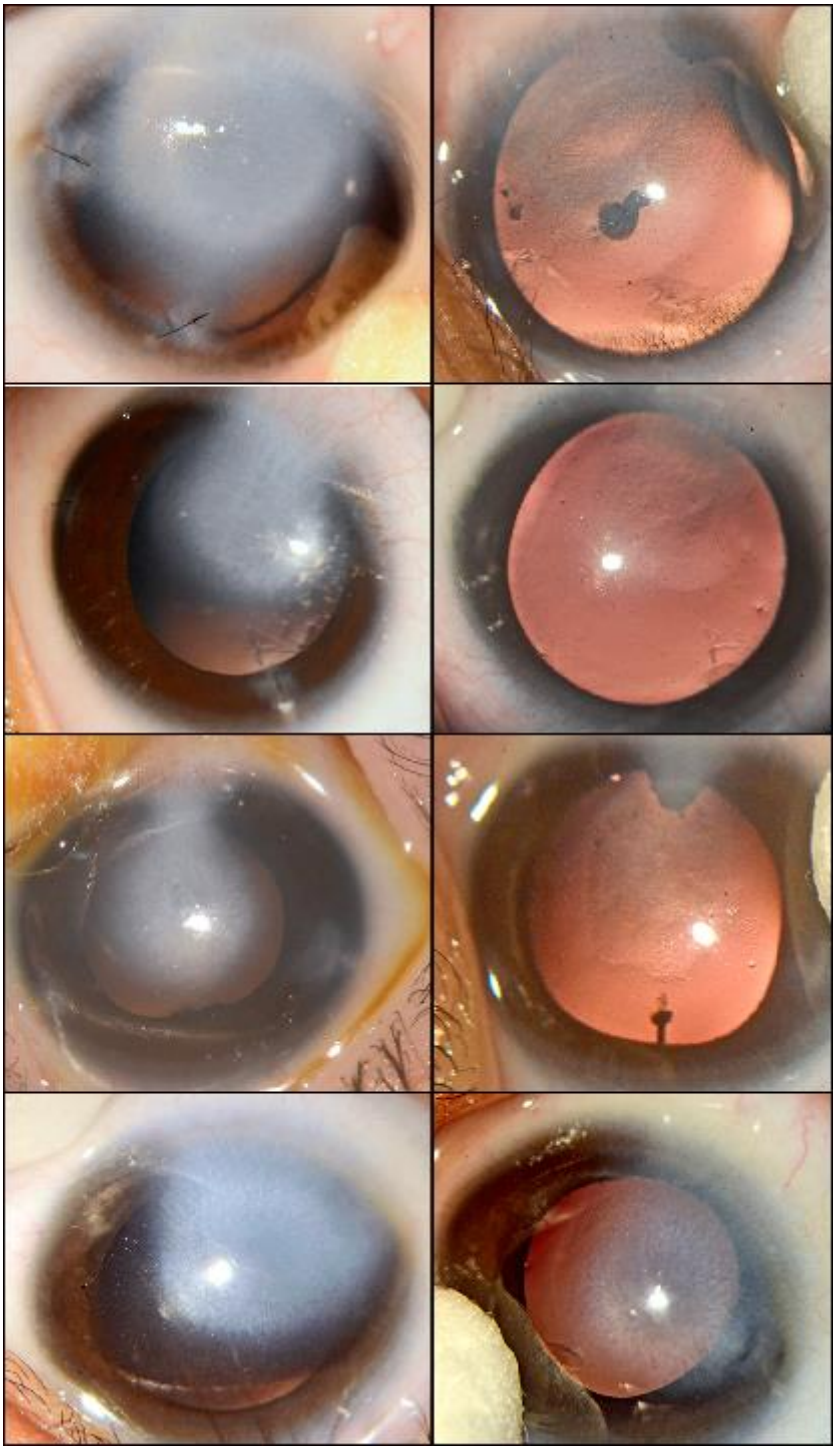

This paper was judged as the BEST PAPER of Cornea - III Session

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NUCLEIC ACID EXTRACTION-FREE CRISPR/CAS12A BASED DIAGNOSTIC PLATFORM FOR FUNGAL KERATITIS

INTRODUCTION:

Fungal diseases are estimated to be responsible for more than 1.6 million deaths annually and over 1 billion people suffer from fungal infections worldwide.[1] Despite the substantial morbidity and mortality associated with fungal infections, they remain an underestimated and neglected global public health problem.[2] Though pathogenic fungi can infect various organ systems of the human body, fungal infections of the eye are particularly devastating for several reasons. Fungal Keratitis (FK) is the most common ocular fungal infection and even in best-case scenarios, the visual rehabilitation and long-term visual outcomes are not optimal.[3–5] Expedient initiation of treatment drastically improves the clinical outcomes with time to diagnosis being one of the most important risk factors influencing morbidity and mortality in ocular and systemic fungal infections.[6,7] However, conventional mycological diagnostic modalities require expertise and are often time-consuming.[3,8] Given the fact that fungal infections disproportionately afflict the rural population in resource-limited settings (RLS), there exists an unmet clinical need for the development of newer diagnostic modalities for rapid and accurate diagnosis of fungal infections.[9]

The rapidity, superior sensitivity and specificity of molecular methods for fungal DNA detection, such as Polymerase Chain Reaction (PCR), have been reported both with ocular and systemic fungal infections.[10–13] Nucleic acid detection techniques are especially advantageous in FK, where the empirical use of antimicrobial therapy decreases the sensitivity of conventional mycological diagnostic techniques.[14] However, PCR remains a high-complexity technique requiring expensive equipment and trained personnel precluding its use in RLS.[15]

Microbial Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and CRISPR-associated (CRISPR-Cas) adaptive immune systems contain programmable endonucleases with distinctive enzymatic properties that can be leveraged for the detection of microbial nucleic acids.[16] Recent studies have highlighted the potential of these CRISPR-based nucleic acid detection methods as rapid and highly sensitive diagnostic modalities to detect pathogenic bacteria and viruses.[17–19] However, the utility of these CRISPR-based diagnostic methods to diagnose fungal infections and their role as a potential diagnostic platform for ophthalmic infections remains to be elucidated.

Here, we describe the development of a rapid, ultrasensitive easy-to-implement CRISPR–Cas12a-based tool, Rapid Identification of Mycoses using CRISPR (RID-MyC), for the detection of fungal nucleic acids. We have also validated our method using contrived reference samples and clinical samples from patients with suspected microbial keratitis.

PATIENTS AND METHODS:

RPA primer and gRNA screening

Small-subunit (18S) rRNA gene sequences from 49 relevant fungal species were accessed via the GenBank database and were aligned by using CLUSTAL Omega.[20] Conserved sequences were identified to generate target

recombinase polymerase amplification (RPA) primers and CRISPR guide RNA (gRNA) sequences. The specificity of the designed RPA primers and gRNA sequences were tested using the PRIMER-Blast Program.[21] The RPA primers were constructed as per manufacturer's instructions and the gRNA sequences were designed within the RPA amplicons based upon the protospacer adjacent motif (PAM) recognized by Cas12a. After screening and optimization, the following RPA primer set and gRNA sequences were identified for validation:

Forward RPA primer: 5'-CGGCACCTTACGAGAAATCAAAGTTTTTGG – 3',

Reverse RPA primer: 5'- ACCACCACCTGAAAAATCAAGAAAGAGCTCTC – 3', and gRNA 5'-UAAUUUCUACUAAGUGUAGAUACUCAACACGGGGAAACUCACCAG – 3'.

Optimization of the RID-MyC Assay

The RID-MyC diagnostic platform combines RPA and CRISPR/Cas12a detection. The RPA reaction was performed as per the manufacturer's instructions (TwistAmp Basic, TwistDx, Cambridge, United Kingdom). The 50µl reaction mixture containing 0.48µM forward and reverse primers, 29.5µl primer free rehydration buffer, 5µl template DNA, and 14mM magnesium acetate (MgOAc) was incubated at 39°C for 30 minutes. LbCas12a trans-cleavage assays were performed similarly to those previously described.[16,18] Briefly, a total of 50nM LbCas12a (New England Biolabs Inc., Ipswich, MA USA) was pre-incubated with 500nM gRNA in 1× NEBuffer 2.1 for 10 minutes at 25 °C. After formation of the RNA–protein complex, 1µM of a quenched fluorescent ssDNA reporter and 13µl of the RPA amplicon were added and incubated at 37°C for 30 minutes or the denoted time in figures. For fluorescence detection, an ssDNA reporter with a 5′ end-labelled FAM group and a 3′ end attached to a Black quencher (/56-FAM/TTATT/3BHQ/) was used. Real-time and endpoint fluorescence was

the raw fluorescence determined by the Real-Time PCR Detection System. Visual detection was accomplished through imaging the tubes in the LED blue light illuminator and the Bio-Rad ChemiDoc MP Imaging System (Bio-Rad., Hercules, CA USA) with its built-in UV channel.

Determination of the specificity and analytical sensitivity of the RID-MyC assay

To determine the specificity and sensitivity of the RPA primers and the RID-MyC, the DNA extracted from cultures of the following organisms isolated from patients with FK was used: *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger*, *Fusarium oxysporum*, *Candida albicans*, *Lasiodiplodia theobromae*, *Alternaria alternata*, *Bipolaris*, *Curvularia*, *Exserohilum*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Escherichia coli*. To determine the sensitivity of the RPA primers, the RPA reactions were performed as described above and the amplified products were investigated using 2% agarose gel electrophoresis (AGE) (eFigure 1). Real-time and endpoint fluorescence detection was used to determine the specificity of the RID-MyC assay using 10 ng DNA of the above listed isolates. The analytical limit of detection (LoD) was evaluated by testing the calibration standards of the following fungal species: *Aspergillus flavus*, *Candida albicans*, *Curvularia* and *Fusarium oxysporum*, prepared by serial dilutions at the following concentrations: 165 fM (10^5 copies), 16 fM (10^4 copies), 1.6 fM (10^3 copies), 165 aM (10^2 copies), 16 aM (10 copies) and 1.6 aM (1 copy).

CLINICAL SPECIMENS

Seventy-five corneal swabs and scrapings from 75 consecutive patients with presumed microbial keratitis presenting to our tertiary eye care facility were collected as previously described.[22,23] Informed consent was obtained from all participants, and the trial conformed to the Declaration of Helsinki.

Ethical approval was obtained from the Institutional Review Board. For the RID-MyC assay and PCR, the affected cornea was swabbed with a sterile polyester tipped applicator (Puritan Medical Products, Guilford, ME, USA) and transferred to a 1.5 ml Eppendorf tube. DNA extraction was performed using the QIAmp DNA Blood Mini kit (Qiagen, Hilden, Germany) and stored at -20°C until further use. The RPA reaction was performed as described above with 10µl of the eluted DNA at 39°C for 30 minutes. LbCas12a trans-cleavage assays were performed as described above. Both real-time and endpoint fluorescence detection was performed for all clinical samples. For the analysis of clinical samples, a RID-MyC assay result was considered positive if it was equal or greater than a cut-off threshold equal to the mean signal of the negative control samples plus three times its standard deviation. Figure 1 illustrates the workflow of the RID-MyC assay for clinical specimens. PCR was performed as previously described and the amplified product was visualized on an UV transilluminator using 2% AGE incorporating 0.5 µg/ml ethidium bromide.[14] Previously described panfungal primers [Forward primer sequence, 5′- GTG AAA TTG TTG AAA GGG AA -3′; and reverse primer sequence, 5′-GAC TCC TTG GTC CGT GTT -3] specific for the 28S rRNA gene were used in our study.

CONVENTIONAL MICROBIOLOGIC INVESTIGATIONS

A standard scraping procedure for corneal debridement was performed for patients with clinically suspected microbial keratitis as previously described.[24] Briefly, two scrapings were smeared directly on separate glass slides for Gram staining and potassium hydroxide (KOH) wet mount, and three further scrapings were taken and directly inoculated onto sheep's-blood agar, chocolate agar, and potato dextrose agar or Sabouraud's agar for bacterial and fungal cultures. Fungal smears were considered positive when fungal elements were seen under low-power magnification and reduced

light. Fungal cultures were considered positive with growth on any two media or moderate to heavy growth on one medium.

STATISTICAL ANALYSIS

Background-subtracted fluorescence was calculated by subtraction of the fluorescence of no-template (water only as "template" input into the RID-MyC reaction) control wells on the plate from target fluorescence values evaluated in the assay run at the same time points in the assay. Statistical significances were analyzed by using Prism 8 (GraphPad Software, version 8.0.1). A *P*-value of < 0.05 was considered statistically significant. The performance indices, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), for the RID-MyC assay was calculated. Sensitivity was defined as the number of eyes with FK detected by the RID-MyC divided by the number of eyes with either KOH smear- or culture-positive for fungus. Specificity was defined as the number of eyes with non-FK detected by the RID-MyC divided by the number of eyes with both smear and culture-negative for fungus. The difference between the performance indices between the test groups was performed using the McNemar test.[25]

RESULTS:

Specificity and Analytical Sensitivity of the RID-MyC Assay

The specificity of the RID-MyC assay determined using DNA isolated from patient isolates demonstrated detection of Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Fusarium oxysporum, Candida albicans, Lasiodiplodia theobromae, Alternaria alternata, Bipolaris, Curvularia, and Exserohilum and no detection of Pseudomonas aeruginosa, Streptococcus pneumoniae, Staphylococcus aureus, Escherichia coli and human DNA, confirming high specificity (eFigures 2, 3). The analytical sensitivity of the

RID-MyC assay was determined and the LoD was 13.8 genomic copies for Aspergillus flavus (eFigure 4), 16.6 for Fusarium solani (eFigure 5), 13.9 for Curvularia lunata (eFigure 6), and 13.3 for Candida albicans (eFigure 7).

RID-MYC ASSAY IN PATIENTS WITH KERATITIS

The results of the RID-MyC assay in correlation with microscopy, culture and PCR for patients with suspected microbial keratitis are shown in Table 1. The real-time fluorescence and visual RID-MyC assay results of the clinical samples are presented in eFigures 8-12. Of the 75 scrapes, 72 (96 %) were positive for fungus by standard mycologic methods of which 55 (73%) were positive by both microscopy and culture and 17 (22.7%) were positive only by microscopy. Between RID-MyC and culture, 56 concordant (52 positive and 4 negative) and 19 discordant (16 RID-MyC positive but culture negative, 3 RID-MyC negative but culture positive) results were observed. All the 16 scrapes positive for RID-MyC but negative for culture were found to be microscopy-positive for fungus. Of the 55 scrapes positive on fungal culture, 36 harbored *Fusarium;* 8 had *Aspergillus*; *Cylindrocarpon* and *Scedosporium* were identified in 2 cultures each*, Lasiodiplodia, Curvularia* and *Exserohilum* were identified in 1 culture each while 4 culture isolates were not speciated. Among the 4 specimens negative by both RID-MyC and fungal culture, 3 showed bacterial growth (*Pseudomonas* in 2 and *Streptococcus* in 1) and one had no growth.

Performance of the RID-MyC assay in comparison to PCR and culture for fungal keratitis

Being a nucleic acid detection modality, the diagnostic performance of the RID-MyC assay was compared to PCR. A sample was considered positive for FK if it demonstrated positive results by culture or microscopy. This definition of positive results was used as the gold standard to calculate and compare the test performances (sensitivity, specificity, PPV and NPV)

between RID-MyC, PCR and culture (Table 2). The sensitivity, specificity, PPV and NPV of RID-MyC were 94.4%, 100%, 100 % and 42.9% respectively. The sensitivity, specificity, PPV and NPV of PCR were 87.5%, 100%, 100% and 25% respectively. There was no significant difference between the sensitivities and specificities of PCR and RID-MyC (p=0.16). The sensitivity, specificity, PPV and NPV of culture were 76.4%, 100%, 100 % and 15% respectively. The sensitivity of RID-MyC was significantly higher than the sensitivity of culture (p=0.002).

DISCUSSION

Here, we combined isothermal amplification and CRISPR-Cas12a to develop a rapid (45 – 60 minutes) and accurate assay for the diagnosis of FK. This is the first study to describe a CRISPR-based assay for the broad range detection of fungal nucleic acids in any system and also the first study to describe a CRISPR-based assay for the diagnosis of ophthalmic infections.

The analytical LoD for fungal nucleic acids of the RID-MyC assay was between 13 -16 genome copies that was similar to the LoD of panfungal PCR targeting the 18s RNA region reported by Gaudio et al.[26] The sensitivity of the RID-MyC (94.4 %) was significantly higher compared to culture (76.4%). Among the 55 fungus-positive scrapes on culture, *Fusarium* (65%) and *Aspergillus* (15%) were the most common isolates. This is in agreement with previous reports from Southern India which have shown that *Fusarium* followed by *Aspergillus* is the most common cause of FK.[27] All the 16 scrapes that demonstrated positive results for fungus by the RID-MyC assay but negative results by culture were positive for fungus by microscopy. This further ascertains the results of several earlier studies that have demonstrated the efficacy of KOH smear over culture for the diagnosis of FK.[28–30] Also, 13 of these 16 patients had received prior antifungal therapy. Bacterial growth was observed in 3 scrapes (*Pseudomonas aeruginosa* in S1

and S73, *Streptococcus pneumoniae* in S6) and all were negative for fungus by RID-MyC assay. No smears demonstrated multiple organisms ("mixed growth") on culture. However, 6 smears demonstrated both fungal filaments and bacteria (Gram negative bacilli in S18, S42 and S75, Gram positive cocci in S6, S10 and S15) on microscopy. Of these 6 samples demonstrating "mixed growth" on microscopy, 5 were positive for fungus by RID-MyC. One sample (S6) that demonstrated both fungal filaments and gram-positive cocci on microscopy, but negative for fungus by RID-MyC grew only *Streptococcus pneumonia* on culture.

Nucleic acid-based diagnostic strategies have become the gold standard for the diagnosis of several infectious diseases.[31] The clinical utility of nucleic acid-based diagnostics relying on PCR or on sequencing have been widely reported for the diagnosis of FK.[13,14,22] Though PCR is still considered to be the gold standard technique for nucleic acid detection, the high cost and requirement of sophisticated equipment and trained personnel precludes its application in RLS where the incidence of ocular and systemic fungal infections is disproportionately high.[15] Isothermal amplification strategies have been able to circumvent the need for thermal cyclers. However, nonspecific amplification decreases their specificity impeding their utilization in real-world settings.[32–34] RID-MyC assay combines the cost effectiveness of isothermal amplification with the sub-attomolar sensitivity of CRISPR-Cas12a systems to create a field-applicable diagnostic for FK. The sensitivity of PCR in this study was similar to the sensitivities reported in previous studies.[35–37] The sensitivity of the RID-MyC assay (94.4 %) was higher compared to PCR (87.5%), though the difference was not statistically significant. However, some key advantages of the RID-MyC assay over PCR include the rapid turnaround time and the integration with accessible and easy-to-use fluorescence-based reporting formats obviating the requirement

for complex laboratory infrastructure. The turnaround time for the RID-MyC assay is only 45-60 minutes compared to approximately 4 hours for PCR. Recently, *in-vivo* confocal microscopy (IVCM) has been demonstrated as a rapid non-invasive diagnosis of fungal infections.[38,39] The sensitivity and specificity of IVCM for the diagnosis of FK is comparable to the RID-MyC assay.[40] However, IVCM still requires expensive equipment and with a steep learning curve to achieve high sensitivity.[38,40]

Greater than 90% of all FK occurs in the developing parts of the world with young adults from rural agrarian communities being predominantly afflicted. Several studies have established that delayed initiation of anti-fungal therapy is one of the predominant factors for treatment failure and irreversible blinding sequelae in FK. A prospective study conducted at a tertiary eye hospital in Nepal identified that distance to the tertiary eye hospital was the predominant cause for delayed presentation in patients with microbial keratitis.[41] Similar studies from Southern India report that patients with fungal keratitis travel a mean distance of 80-120 miles to access eye care and that the costs for accessing eye care contributed to a significant portion of the total costs incurred by the patients.[42]

Corneal smears and culture are considered to be the current gold standard for the diagnosis of FK. However, culture lacks sensitivity, is time consuming and requires at least 48-72 hours to establish a diagnosis.[43] Microscopy is a rapid, inexpensive, sensitive and specific diagnostic test but still requires clinical expertise and equipment for obtaining corneal scrapings and considerable mycological skill and knowledge for prompt identification of fungal hyphae and to rule out artefacts and contaminants. Given the above facts, the need for tertiary care facilities to diagnose FK remains the bottleneck which precludes the management of FK at the primary health care level. Our advancements with the development of the RID-MyC assay could

fill significant gaps in the diagnosis of FK by establishing a point-of-care (POC) test which could enable the management of FK at the primary health care level.

Limitations of this assay include those intrinsic to all nucleic acid detection platforms including the possibility of detecting nonviable fungi. Though simple visualization of test results greatly improves the ease of use of the RID-MyC assay, sample preparation and DNA extraction is still required which increases the complexity of the procedure and potentially limiting its use as a POC test. However, other CRISPR-based diagnostic systems have optimized nucleic acid extraction-free lyophilized one-pot reactions for the diagnosis of infectious diseases which can be utilized to improve the field deployability of the RID-MyC assay.[44] One patient with an unidentified dematiaceous fungus on culture was not detected by the RID-MyC assay. Further large-scale studies in different geographical regions may be necessary to evaluate the versatility of the RID-MyC assay in detecting various pathogenic fungal species. Another limitation of the RID-MyC assay in its present form is the inability for species differentiation. However, the use of Cas12 effectors in this assay provides the opportunity to expand the capability of the RID-MyC assay to perform multiplexed and sensitive assays for the differentiation of fungal species.[17] Additionally, the RID-MyC assay targets the 18s rRNA region of the fungal genome which has been previously reported as an effective target for species-level differentiation of medically important fungi. Another limitation of this study was the dominance of filamentary fungal keratitis, the relatively low proportion of bacterial infections and the absence of *Candida* keratitis, which is more common in temperate climates.

CONCLUSION:

In summary, the RID-MyC assay for diagnosis of FK is a promising addition to the existing diagnostic armamentarium and will potentially enable POC testing of FK in RLS. Considering that expedient and accurate diagnosis is a huge unmet need for other localized and systemic fungal infections, we believe that the results of this study would catalyze the application and development of CRISPR-based assays for the diagnosis of other invasive fungal infections.

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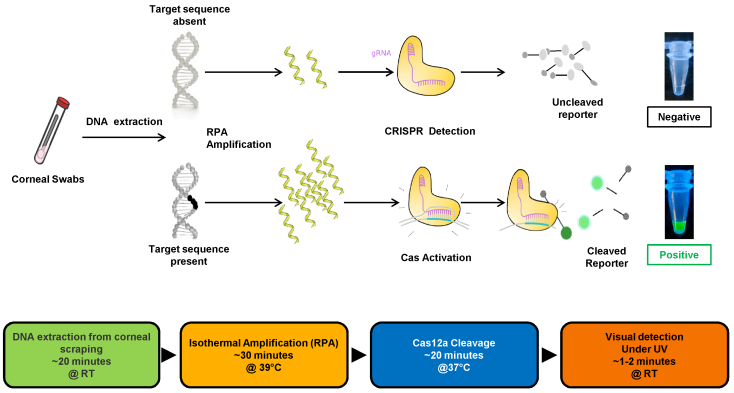
Figure 1: Schematic of RID-MyC assay.



Legend: Figure 1:

Figure 1 shows schematic of RID-MyC assay.

Abbreviations: RPA – Recombinase Polymerase Amplification, CRISPR – Clustered Regularly Interspaced Short Palindromic Repeats, Cas12a – CRISPR associated protein 12a, RID-MyC – Rapid Identification of Mycoses using CRISPR, UV – Ultraviolet, RT - Room Temperature.

Table 1: Results of microscopic examination, culture, PCR, and RID-MyC assay in Microbial Keratitis samples

Table 1: Results of microscopic examination, culture, PCR, RID-MyC assay in Microbial Keratitis samples

S. No.	Diagnostic Method			
	Microscopic Examination*	Bacterial and Fungal Culture	PCR	RIDMyC
S1	GNB	Pseudomonas aeruginosa	NEG	NEG
S2	Filaments	Fusarium	POS	POS
S3	Filaments	NEG	POS	POS

S4	Filaments	Aspergillus flavus	POS	POS
S5	Filaments	Fusarium	POS	POS
S6	GPC, Filaments	Streptococcus pneumoniae	POS	NEG
S7	Filaments	NEG	POS	POS
S8	Filaments	Fusarium	POS	POS
S9	Filaments	Fusarium	POS	POS
S10	GPC, Filaments	NEG	NEG	POS
S11	Filaments	Fusarium	POS	POS
S12	Filaments	NEG	NEG	POS
S13	Filaments	Fusarium	POS	POS
S14	Filaments	Aspergillus	POS	POS
S15	GPC, Filaments	Fusarium	NEG	POS
S16	Filaments	Unidentified dematiaceous fungi	POS	NEG
S17	Filaments	Scedosporium	POS	NEG
S18	GNB, Filaments	Aspergillus fumigatus	POS	POS
S19	Filaments	NEG	NEG	POS
S20	Filaments	Fusarium	POS	POS
S21	Filaments	Fusarium	POS	POS
S22	Filaments	Aspergillus flavus	POS	POS
S23	Filaments	Fusarium	POS	POS
S24	Filaments	NEG	POS	POS
S25	Filaments	Fusarium	POS	POS
S26	Filaments	Lasiodiplodia	POS	POS
S27	Filaments	Fusarium	POS	POS
S28	Filaments	Fusarium	POS	POS

S29	Filaments	NEG	POS	POS
S30	Filaments	NEG	POS	POS
S31	Filaments	Unidentified fungal colonies	POS	POS
S32	Filaments	Fusarium	POS	NEG
S33	Filaments	Unidentified fungal colonies	POS	POS
S34	Filaments	Unidentified fungal colonies	POS	POS
S35	Filaments	NEG	POS	POS

Table 1: Results of microscopic examination, culture, PCR, RID-MyC assay in Microbial Keratitis samples (continued)

S. No.	Diagnostic Method			
	Microscopic Examination*	Bacterial and Fungal Culture	PCR	RIDMyC
S36	Filaments	Fusarium	POS	POS
S37	Filaments	Fusarium	POS	POS
S38	Filaments	Fusarium	POS	POS
S39	Filaments	Fusarium	POS	POS
S40	Filaments	Fusarium	POS	POS
S41	Filaments	Curvularia	POS	POS
S42	GNB, Filaments	NEG	NEG	POS
S43	Filaments	Fusarium	POS	POS
S44	Filaments	NEG	NEG	POS
S45	Filaments	Fusarium	POS	POS
S46	Filaments	NEG	POS	POS

S47	Filaments	Aspergillus	POS	POS
S48	Filaments	Aspergillus flavus	POS	POS
S49	Filaments	Fusarium	POS	POS
S50	Filaments	Aspergillus flavus	POS	POS
S51	Filaments	Fusarium	POS	POS
S52	Filaments	Aspergillus flavus	NEG	POS
S53	Filaments	Fusarium	POS	POS
S54	Filaments	Fusarium	POS	POS
S55	Filaments	NEG	POS	POS
S56	Filaments	Fusarium	POS	POS
S57	Filaments	Fusarium	POS	POS
S58	Filaments	Cylindrocarpon	POS	POS
S59	Filaments	Fusarium	POS	POS
S60	Filaments	Fusarium	POS	POS
S61	Filaments	Fusarium	POS	POS
S62	Filaments	Scedosporium	POS	POS
S63	Filaments	Fusarium	POS	POS
S64	Filaments	NEG	POS	POS
S65	Filaments	NEG	POS	POS
S66	Filaments	Fusarium	POS	POS
S67	Filaments	Fusarium	POS	POS
S68	Filaments	NEG	POS	POS
S69	Filaments	Cylindrocarpon	NEG	POS
S70	Filaments	Fusarium	POS	POS
S71	Filaments	Fusarium	NEG	POS
S72	Filaments	Exserohilum	POS	POS
S73	GNB	Pseudomonas aeruginosa	NEG	NEG

Table 1: Results of microscopic examination, culture, PCR, RID-MyC assay in Microbial Keratitis samples (continued)

S. No.	Diagnostic Method			
	Microscopic Examination*	Bacterial and Fungal Culture	PCR	RIDMyC
S74	GPC	NEG	NEG	NEG
S75	GNB, Filaments	Fusarium	POS	POS

*- Includes results of both potassium hydroxide wet mount and Grams' stain

Abbreviations: PCR – Polymerase Chain Reaction, RID-MyC – Rapid Identification of Mycoses using CRISPR, CRISPR – Clustered Regularly Interspaced Short Palindromic Repeats, GNB – Gram Negative Bacilli, GPC – Gram Positive Cocci, POS – Positive (PCR/RID-Myc), NEG – Negative (PCR/RID-Myc), No Growth (Culture).

Table 2: Performance of PCR, RID-MyC assay and culture in comparison to reference standard in microbial keratitis samples

Table 2: Performance of PCR, RID-MyC assay and culture in comparison to reference standard
in microbial keratitis samples

Results (n = 75)	Reference Standard*		Performance of Assay				
	Positive	Negative	% Sensitivity	% Specificity	% Positive Predictive value	% Negative Predictive value	p-value
PCR			87.5 (77.6 - 94.1)	100 (29.2 - 100)	100	25 (15.3 - 38.1)	

Positive	63	0					
Negative	9	3					
RID-MyC			94.4 (86.4 - 98.5)	100 (29.2 - 100)	100	42.9 (22.4 - 66)	0.16 ˜
Positive	68	0					
Negative	4	3					
Culture			76.4 (64.9 - 85.6)	100 (29.2 - 100)	100	15 (10.4 - 21.1)	0.002 †
Positive	55	0					
Negative	17	3					

*Reference Standard - Includes results of both microscopy and culture; considered positive if either was positive. Values within brackets in performance parameters indicate 95% Confidence Interval. ˜ - Indicates *p*-value between PCR and RID-MyC † - Indicates *p* - value between RID- Candculture Abbreviations: PCR – Polymerase Chain Reaction, RID-Myc – Rapid Identification of Mycoses using CRISPR, CRISPR – Clustered Regularly Interspaced Short Palindromic Repeats

This paper was judged as the BEST PAPER of Diabetic Retinopathy & Medical retina – I Session

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COATS DISEASE IN INDIA: CLINICAL FEATURES, TREATMENT AND OUTCOMES IN PATIENTS OLDER THAN FIFTY YEARS

ABSTRACT

Purpose: To study the clinical profile, treatment, and outcomes of patients diagnosed with coats disease in India with age greater than 35 years.

Methods: Cross-sectional, observational hospital-based study of patients with adult-onset coats disease.

Results: A total of 74 eyes diagnosed with adult-onset coats disease were included. Mean age of presentation was 49.5 years (range….). Majority were males (74%) with unilateral presentation (86%). The most common stage as per Shields classification was extra-foveal exudation (2A; 39%) followed by foveal exudation (2B; 34%). Treatment administered…….(laser, injections, cryo etc). Anatomical outcomes…….Mean best corrected visual acuity pre and post operative period, improvement in terms of Snellen visual acuity or logMAR. The mean follow-up period…….

Conclusion: Adult-onset coats disease patients have unilateral presentation with less severe stage when compared with childhood variant. Despite good anatomical response, the final visual acuity results are limited.

INTRODUCTION

Coats disease is a rare idiopathic retinal vasculopathy characterized by retinal telangiectasia with intraretinal and/or subretinal exudation leading to exudative retinal detachment in the absence of retinal or vitreal traction. [1] It is a progressive retinal disease that is usually unilateral (95%) and usually affects young males (76%).

In 2001, Shields et al. proposed a five-stage classification for Coats disease based on clinical features. [2]

In a cross-sectional observational hospital-based analysis of 690 eyes conducted by our network, we showed that in India, the mean age of presentation was 16.8 years, 71.4% patients presented in the first 2 decades of life, 75.3% patients were male and 97.8% had unilateral affliction. [3]

Small subset of coats disease may present later in adulthood. 17.2% patients from our study belonged to the 4th decade of life or older. [3]

Smithen et al described the onset of Coats disease in individuals greater than 35 years of age, where the disease was mostly unilaterally, primarily seen in men, had vascular telangiectasia, lipid exudation, microaneurysms and macroaneurysms, macular edema, areas of capillary non-perfusion with adjacent webs of filigree like capillaries, and an absence of retinal neovascularization. Patients often presented with good vision, without leukocoria, extensive areas of exudation and retinal detachment. [4]

In an analysis of patients diagnosed with Coats disease in adulthood in south India, similar findings were noted, with lesser incidence of retinal detachment, and lesser quadrants of retinal involvement than pediatric eyes. [5]

The aforementioned studies are either from the western hemisphere [4], or from a time period (1995-2012) [5] without widespread use of wide field

angiography, availability of anti-VEGF injections, and microincisional vitrectomy.

In this study, we describe the clinical profile, treatment, and visual outcomes of Coats disease in patients greater than 34 years of age presenting to a multi-tier ophthalmology hospital network in India using the electronic medical records (EMR) system.

MATERIALS AND METHODS

Study design, period, location, and approval

This cross-sectional observational hospital-based study included all patients presenting between August 2010 and January 2021 to a multi-tier ophthalmology network located in India [7]. The patient or the parents or guardians of the patient filled out a standard consent form for electronic data privacy at the time of registration. The clinical data of each patient who underwent a comprehensive ophthalmic examination was entered into a browser-based electronic medical records system (eyeSmart EMR) by uniformly trained ophthalmic personnel and supervised by an ophthalmologist using a standardized template [8]. The study adhered to the Declaration of Helsinki and was approved by the Institutional Ethics Committee.

CASES

In the study period between August 2010 and January 2021, 690 eyes were identified to have Coats disease in one or both eyes (ICD H35.0). [3]

119 eyes were diagnosed to have Coats disease with onset in the 4th decade of life onwards, and were further analyzed for demographic details, clinical features, treatment modalities and outcomes.

Only those eyes were included in the study which were treatment naïve, and confirmed to have Coats disease of adult onset on the basis of clinical

examination, fundus fluorescein angiography and ocular coherence tomography. A total of 74 eyes from 69 patients were diagnosed with Coats disease with onset of disease after 34 years of age.

DATA RETRIEVAL AND PROCESSING

The data of 69 patients included in this study were retrieved from the electronic medical record database and segregated into an excel sheet. The excel sheet with the required data was then used for analysis using the appropriate statistical software. The visual acuity was classified according to the WHO guidelines [9]. The subjective measurement of visual acuity was done using the Snellen visual acuity chart). Coats disease staging was based on the clinical staging scheme described by Shields et al as stage 1 (only retinal telangiectasia), stage 2A, (telangiectasia and extrafoveal exudation), stage 2B (telangiectasia and foveal exudation), stage 3A1 (subtotal extrafoveal exudative retinal detachment), stage 3A2 (subtotal exudative retinal detachment involving the fovea), stage 3B (total exudative retinal detachment), stage 4 (total exudative retinal detachment and secondary glaucoma), or stage 5 (advanced end-stage disease, phthisis bulbi) [2].

The columns included the data on patient demographics, clinical presentation, ocular diagnosis, stage of disease, fundus fluorescein angiography features, ocular coherence tomography findings, treatment provided and follow up information, and were exported for analysis.

Outcomes were analyzed at the last follow up visit in terms of visual acuity change. The change in the stage of the disease was classified as follows:

1. Improvement: When disease shows response to treatment with decrease in severity as per the Shields classification

2. Resolved: When disease shows response to treatment, with involution of all abnormal vessels, macular edema as well as sub-retinal fluid.

3. Worsened: When disease severity increases as per the Shields classification or if subfoveal hyper reflective nodule develops.

4. Stable: No change in disease severity as per the Shields disease classification.

Statistical analysis

RESULTS

Age

The mean age of the patients was 49.6 years (35 years-75 years) while the median age was 47.5 (IQR: 19) years. The most common age group of the patients were distributed between 35 and 44 years (*n* = 32, 43.2%) followed by 55 and 64 years (n = 18, 24.3%). Table 1 lists the detailed distribution of all age groups and the staging at each group.

Gender

There were 50 male (73.52%) and 19 female (27.53%) patients, with a male: female ratio of 2.63.

Laterality

Of the 69 patients affected, 64 (92.75%) had unilateral presentation, whereas 5 patients (7.25%) suffered from bilateral disease at presentation.

Presenting Visual Acuity

In the 74 eyes, 24 (32.4%) eyes had mild or no visual impairment (20/20 to 20/70), 18 (24.3%) eyes had moderate visual impairment (< 20/70 to 20/200), 9 (12.1%) eyes had severe visual impairment (< 20/200 to 20/400), and 23 (31%) were classified as blind with vision of 20/400 or worse.

STAGING OF COATS DISEASE

Amongst the 74 eyes, the most common stage was extra-foveal exudation (2A; 39.18%) followed by; foveal exudation (Stage 2B; 33.7%); foveal retinal

detachment (Stage 3A2; 12.1%); Telangiectasia (Stage 1; 5.4%); extra-foveal retinal detachment (Stage 3A1; 4%); neovascular glaucoma (Stage 4; 4%) and total retinal detachment (Stage 3B; 1.3%).

CLINICAL FEATURES

Amongst the clinical features noted, the most common clinical features included microaneurysms (60 eyes, 81%), cystoid macular edema (35 eyes, 47.2%) and subretinal fluid (19 eyes, 25.6%).

Ocular Coherence Tomography

Ocular coherence tomography was performed for 40 eyes, with the Zeiss Cirrus 6000 (ZEISS, Dublin, CA) Triton SS OCT (Topcon Medical Systems Europe, Milano, Italy) and Spectralis SD OCT (Heidelberg Engineering GmbH, Germany). The most common findings noted were presence of intraretinal fluid in 32 eyes (80%), hard exudates in 31 eyes (77.5%) and disorganized retinal inner layer in 22 eyes (55%). Disruption of the outer retinal layers was noted in 14 eyes (35%) while subfoveal nodule was seen in 7 eyes (17.5%).

TREATMENT

Of the 74 eyes, 58 eyes that had adequate follow up were included for the analysis. 53 eyes were treated, while 2 were kept on observation and 3 were deemed best not treated. 16 eyes were lost to follow up. The mean period of follow up of 111.74 weeks (0-1171) was noted. 23 (43.3%) eyes were treated with laser alone, 1 eye (1.8%) underwent solely cryotherapy, 1 eye (1.9%) required combined laser and cryotherapy and 1 eye (1.8%) was treated with cryotherapy and trans pupillary thermotherapy. 21 eyes (39.6%) were treated with adjuvant intravitreal agents (anti-VEGF and steroids) along with ablative therapy. 2 eyes (3.8%) required IOP reduction measures in the form of anterior retinal cryopexy and trans scleral cyclo photocoagulation.

The mean sessions of sole laser and cryotherapy were 1.5 per eye. When combined with intravitreal adjuvants 2 sessions of ablative therapy were required per eye. Overall 1.7 sessions of laser and /or cryotherapy were needed.

OUTCOMES

Of the 58 eyes followed up over 111.74 weeks, 24 (41.3%) eyes had mild or no visual impairment (20/20 to 20/70), 11 (18.9%) eyes had moderate visual impairment (< 20/70 to 20/200), 6 (10.3%) eyes had severe visual impairment (< 20/200 to 20/400), and 17 (29.3%) were classified as blind with vision of 20/400 or worse.

COMPLICATIONS

Of the 74 eyes, 15 were lost to follow up. Amongst the 59 patients followed up for a mean time of 111.74 weeks, 8 eyes developed a subretinal nodule (13.7%), 4 eyes had neovascular glaucoma (6.8%), while 1 eye was painfully blind (1.7%).

DISCUSSION

Coats disease is a rare, non-hereditary retinal disease with no associated systemic abnormalities or racial predilection. A population-based study from the UK on 55 cases revealed the estimated population-based incidence of 0.09/100,000 persons. [10]

In our series, the overall hospital-based prevalence of Coats disease between 2010 and 2021 (10-year period) was 0.025% of all eye diseases with 2/3rd of patients in age group below 20 years. Only 17.2% of these patients presented from the 4th decade of life onwards, with a successive decrease in prevalence in each decade of life, highlighting the rare nature of Coats disease and its greater rarity in older individuals.

Only few population based studies on Adult onset Coats disease have been published in literature, highlighting the importance of our findings. [4- 6]

In Rishi et al's retrospective analysis of 646 patients with Coats disease from south India, seen between January 1995 and January 2012, only 48 eyes had onset of Coats disease after 34 years of age. [5]

In our overall analysis of Coats disease, almost universally the patients had unilateral disease (97.8%) and were of male gender (75.3%). However in the current cohort of older patients, 7.25% had bilateral disease. Males had a similar predominance comprising 73.52% of all patients. Similar findings of greater incidence of bilateral disease was seen in Rishi et al's study from South Asia [5] but not from Smithen's sudy from western subjects. [4]

The most common stage of disease presentation was stage 2A (39.18%) and stage 2B (33.7%). Only 13 eyes (17.4%) presented with stage 3 disease, of which just 1 eye had a total retinal detachment (1.3%). This is unlike the disease severity when we include pediatric eyes. Our previous study [3] had more prevalence of stage 2B (23.3%) and Stage 3A (22.4%). Approximately 1/3rd of eyes had a retinal detachment. It has been seen in studies that higher aqueous concentration of VEGF and interleukins correlates with disease severity, and that pediatric eyes have significantly greater aqueous load of VEGF than adult eyes with Coats disease. [11]

4 patients of retinitis pigmentosa developed a Coats like response, and were included in the study cohort. All four had unilateral exudative vitreoretinopathy, had a male: female ratio of 1:1 and mean age of presentation of 43.75 years. All patients were legally blind, despite none having a retinal detachment, or glaucoma. Coats like response is known to occur in 5% of eyes with retinitis pigmentosa, with a mean age of diagnosis of exudation occurring a decade after the diagnosis of retinitis pigmentosa.

Such patients were seen to have a bilateral response of exudation, affecting the peripheral retina. [12]

Amongst our study population, we also had 2 patients who developed Coats retinopathy, after receiving treatment for vasculitis and branch retinal vein occlusion respectively elsewhere in the past with laser photocoagulation. Coats like response is a rare complication, seen in eyes with prior history of laser therapy. [13]

When analyzing the OCT results we see that the most commonly seen abnormality is the presence of intraretinal fluid and hard exudates. However also seen were the presence of DRIL and broken ellipsoid zone and external limiting membranes. These biomarkers have been noted to occur in other retinal vasculopathies, with negative correlation with visual acuity. [14] This also points to the underlying vascular insufficiency in eyes with Coats disease, and high degree of macular involvement at the capillary level, irrespective of the quadrant of involvement at gross clinical examination.

Other peculiar features noted on OCT was the pattern of tall tented central macular edema, similar to that seen in vein occlusions, as well as presence of schitic changes, appearance of ring of pearls sign and epiretinal membrane formation. [15]

The prior studies on adult onset Coats disease did not examine the impact of intravitreal agents on treatment outcomes. The management of Coats disease varies with the age at presentation and stage of the disease. Initial disease is managed with laser or cryotherapy. Assosciated macular exudation, edema or sub retinal fluid was treated with adjuvant intravitreal anti-VEGF agents, triamcinolone Acetonide or Ozurdex. Sole laser ablation was the most common method of treatment in our study population (43.3%) while just three eyes needed sole or additional cryotherapy (5.7%). 39.6% eyes needed adjuvant intravitreal agents. None of the eyes needed additional

surgical procedures to drain the fluid or needed enucleation. The higher use of sole laser photocoagulation, and lack of surgical intervention is in contrast to our findings in the previous study which comprised of predominantly pediatric patients. [3]

Of the 58 patients followed up for 111.7 weeks, only 39.6% showed resolution of the disease. Approximately half the eyes remained stable (44.6%). Both pre and post treatment, mean visual acuity of did not change.

The limitations of our study are as follows. Firstly, the retrospective nature of the data set. Our study is a hospital-based study which included only the patients who presented or were referred for an eye examination. Due to this nature, it must be emphasized that this study is not a true representative of the entire Indian population. Nevertheless, it provides insight into the burden of Coats disease in India. Second, we do accept variation in clinical decision and surgical practice among multiple retina specialists managing these cases over the course of the disease. The results of this paper would help us to formulate guidelines for uniform data documentation and identify risk factors influencing prompt referral to retina specialist.

CONCLUSION

Coats disease in rare instances presents in older individuals. Such cases have greater prevalence of bilateral disease, with a male predominance. Unlike pediatric eyes, they present with lesser prevalence of retinal detachment. They generally are treated with laser photocoagulation, and in our study population did not require surgical intervention or enucleation for even a single case. Older individuals with Coats like retinopathy may have history of laser photocoagulation or may have retinitis pigmentosa.

OCT and fluorescein angiography can play a crucial role in diagnosis and prognostication. Majority of cases remain stable or resolve. However visual benefits post-surgery are limited.

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This paper was judged as the BEST PAPER of Diabetic Retinopathy & Medical retina – II Session

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NOVEL MOLECULE MEDIATED INHIBITION OF ICAM AS TARGET FOR DIABETIC VASCULAR LEAKAGE : PRECLINICAL TRIAL

Novel Small molecule mediated inhibition of intercellular adhesion molecule (ICAM-1) mediated effects as a potential target for diabetic vascular leakage: A pre-clinical efficiency trial

PURPOSE

Diabetic macular edema (DME) is currently treated with intravitreal Anti-VEGF and/or steroids. Since adhesion molecules have been associated with the pathology of diabetic retinopathy, we hypothesised that ICAM-1 modulation may modulates DR pathology in vivo. Thus, we tested the effect of intravitreal injection of a small molecule which inhibits the ICAM-1 mediated effects and compared its efficacy with intravitreal Ranibizumab in prevention of vascular leakage in a STZ induced diabetic mouse model as a potential for treatment of DME.

INTRODUCTION:

Diabetic Macular oedema and Proliferative changes induced by Diabetic retinopathy are the common complications of Diabetes Mellitus and are a leading cause of preventable blindness in the adult working population.

Hyperglycemia is a critical factor in the etiology of diabetic retinopathy and initiates downstream events including: basement membrane thickening, pericyte loss and retinal capillary non-perfusion. The focus has been recently directed to the molecular basis of the disease process in regards for novel treatment targets. (Figure 1) Various molecular pathways have been identified as pathologic in DR and DME including inflammation, oxidative stress, autophagy, angiogenesis, adaptive immune responses, etc.

The role of inflammation in diabetic retinopathy is both prominent as well as complex. While hyperglycaemia, oxidative stress, advanced glycation end product formation all contribute to inflammation, the inflammatory response itself propagates these pathways further. There is a significant increase in the systemic and local, intraocular expression of proinflammatory cytokines, activation of soluble and cell surface adhesion molecules, and the expression of chemokines in the retinae of patients with diabetic retinopathy.(1)

ICAM-1 is a immunoglobulin-(Ig)-like transmembrane glycoprotein expressed on the surface of leukocytes, endothelial cells, and epithelial cells. It influences the adhesion of circulating immune cells to the endothelium and contributes to immune cell migration and perivascular infiltration. Soluble ICAM-1 engages with receptors on various cellular surfaces and initiates a signal transduction program inherent in disease pathologies. Increased levels of ICAM-1 and its ligands have been observed in patients with DR and retina of animal models.(2)(3)(4)

In our study we evaluated the effect of intravitreal injection of a small molecule which inhibits the ICAM-1 function versus intravitreal

Ranibizumab in prevention of vascular leakage in a Streptozotocin (STZ) induced diabetic mouse model.

We further hypothesize that these dysregulated factors either augment the VEGF dependent or VEGF independent vascular leakage and angiogenesis.

MATERIALS AND METHODS

After institutional ethics committee approval, aqueous humour about 50 micro litres was collected in patients who were undergoing intravitreal injection for diabetic macular oedema.

Soluble factor profiling of aqueous humor from patients with diabetic retinopathy and DME undergoing intravitreal injection showed elevated levels of pro-angiogenic and proinflammatory cytokines. Elevated levels of sICAM noted in the aqueous humor of non-responder group (based on OCT classification- less than 100 micron decrease or increase in central macular thickness after three intravitreal anti-VEGF injection).

Based on the profiling data we chose to further investigate the role of ICAM in both cellular and animal models for proof of concept.

Retinal pigment epithelium and endothelial cells are responsible for the maintenance of blood retinal barrier and development of neovascularization, hence were considered for in-vitro cellular model. The cell lines were subjected to stressors such as hyperglycemia and hypoxia which resulted in overexpression of ICAM on cell surface necessitating further exploration of sICAM role in disease pathology and as treatment target.

The in-vivo arm of the study involved streptozotocin induced diabetic rat models with diabetic retinopathy. The body weight of the various treatment groups of STZ mice was constant throughout the study. There was an increase in the random blood glucose levels in the plasma of the STZ induced diabetic rats and remained elevated throughout the study compared to control non STZ mice.

After induction period of 20 weeks post STZ intraperitonial injection, retinal changes are evident in the animal eyes. The rats were treated by an intra vitreal injection of RWJ-LFA-1 ICAM-1 functional antagonist in one group and another group received Ranibizumab. Two weeks post intravitreal injection, the rats were injected with fluorescein isothiocyanate (FITC) dextran in their tail vein and sacrificed. The retinal flat mounts were prepared and studied.

The functional readouts were vascular leakage and the molecular readouts were mRNA expression and secretion of pro and anti-inflammatory and angiogenic factors.

RESULTS:

The RWJ-LFA-1 antagonist treated eyes and ranibizumab treated eyes showed significant and comparable reduction in the leakage patterns which demonstrates sICAMs role in vascular leakage in diabetic retinae. (Figure-2)

Further mRNA expression of the all the pro-inflammatory and pro-angiogenic genes was increased in diabetic, (STZ treated) mouse retinas , which was similar to what was also seen in the aqueous from human subjects who had DME. ICAM-1, IL-6 and PEDF expression is reduced post RWJ -LFA-1 antagonist treatment compared to mock treated diabetic rat

retinas. Expression of VEGF and MCP-1 was unaffected in RWJ treated retinae which indicates that ICAM works independent of VEGF expression and has role in vascular leakage. Anti-VEGF is able to achieve reduction in mRNA expression of all genes to varying levels. (Figure-3)

CONCLUSION:

Anti-VEGF treated and RWJ-LFA- 1 antagonist treated retinae both phenotypically express reduced vascular leakage. This translational study shows that RWJ-LFA-1 antagonist is a potential drug target which can be used as a novel treatment option for DME.

ICAM-1, IL-6 and PEDF m-RNA expression is reduced post RWJ -LFA-1 antagonist treatment than the diabetic rat retinas although not as significant as anti VEGF treated retinae, which may be due to the dosage used or the mechanism of action. This is further explained by the action of anti vegf on gene expression of proteins whereas RWJ-LFA-1 acts on further interaction of secreted protein. This also indicates that sICAM can either augment the VEGF dependent or VEGF independent vascular leakage and angiogenesis and has a different molecular pathway than VEGF and role in pathological process.

Although more robust animal data is needed before this can be translated to phase-1 clinical trials, we believe that molecular biomarkers research can yield innovative and novel treatment targets for DME and vascular leakage.

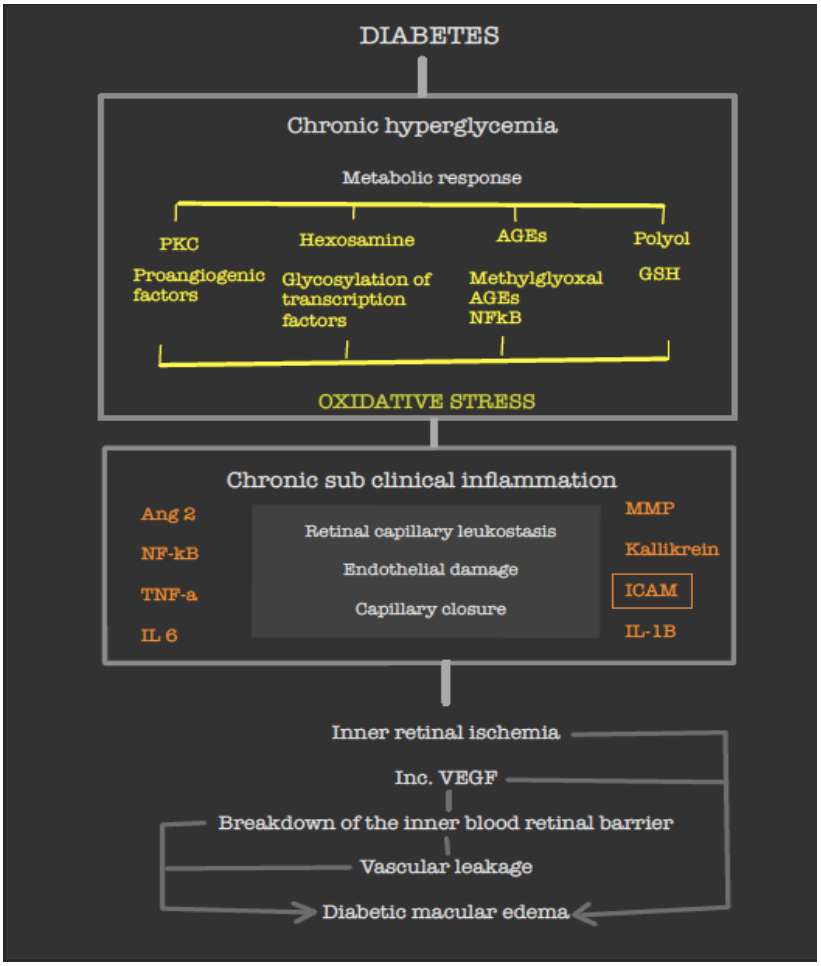

Figure 1: Pathophysiological events in diabetic retinopathy

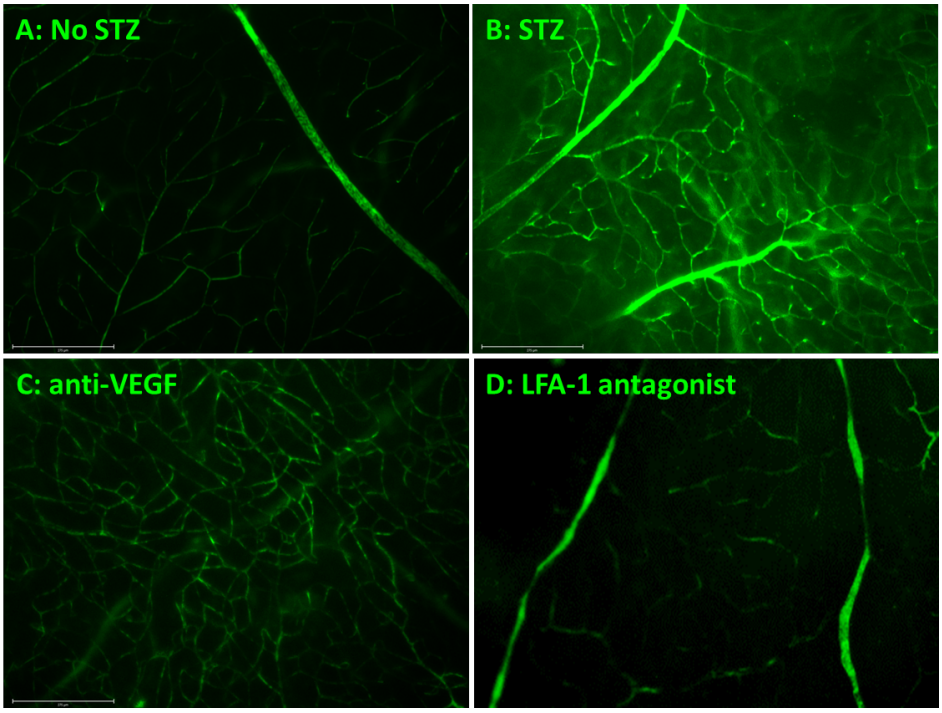

Figure 2.Retinal flat mounts of experimental rats-

a. Non diabetic rats, b. Streptozotocin induced diabetic rats, c. STZ induced diabetic rat with anti-VEGF(Ranibizumab) and d. Diabetic rats with LFA-1 antagonist

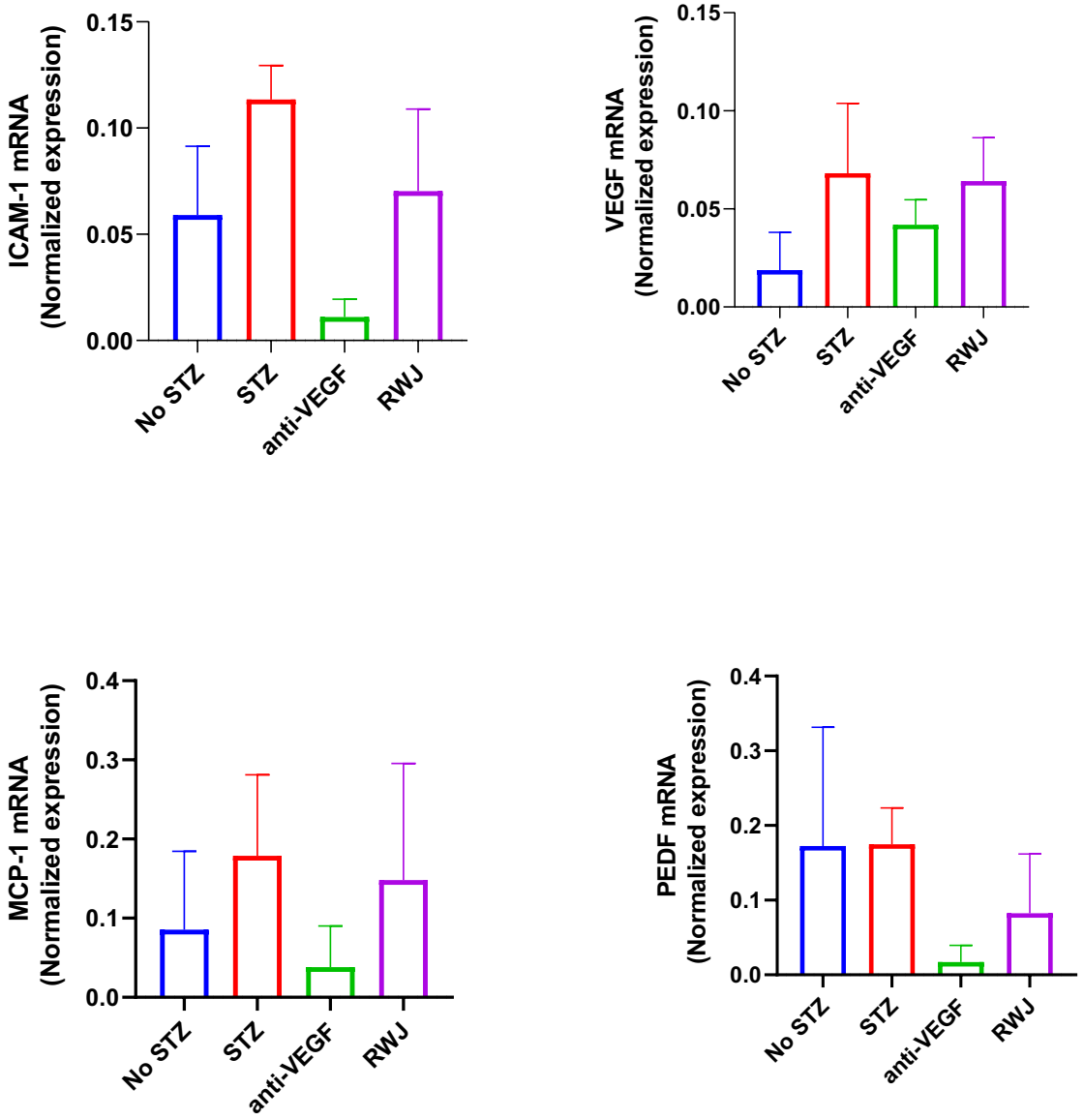

Figure-3: mRNA expression of pro-angiogenic and anti-angiogenic genes in retinae of the experimental animals

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This paper was judged as the BEST PAPER of External Disease Session

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TOPICAL HUMAN IMMUNOGLOBULIN AS ADJUNCT THERAPY IN REFRACTORY DRY EYE DISEASE

ABSTRACT

Aim: To evaluate adjunct topical human immunoglobulin IgG (IVIG) therapy in refractory inflammatory dry eye disease (DED).

Method: Prospective longitudinal comparative open-label study of adjunct topical human IVIG in 30 cases of DED and 30 cases on conventional treatment taken as controls. Study parameters included dry eye severity level, TBUT, Schirmer's, corneal & conjunctival staining score (CFS & CSS), OSDI at baseline & 6-months follow-up (FU).

Result: In 47 of 56 eyes with 6-month-FU, mean OSDI (69.5±14.3), Schirmer's (8.8±8.5), CFS (5.2±3.8), CSS (5.8±3.4), FTBUT (3.7±3.2)] showed significant improvement at 3&6 month-FU [OSDI 0.003/<0.001, Schirmer's <0.001/<0.001, CFS <0.001/0.0002, FTBUT <0.001/<0.001 & CSS 0.0627/0.008(improved at 6 months). There was reduction in topical lubricant & steroid therapy. Among 42 eyes (21 patients) of controls, 38.09% (16 eyes) showed improvement at 6 month-FU.

Conclusion: Adjunct topical IVIG therapy is effective in controlling ocular surface inflammation & reducing steroid dependency in refractory inflammatory DED.

INTRODUCTION

The TFOS DEWS II Definition and Classification Subcommittee [1] elaborates the definition of dry eye disease (DED) as "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles." The impact of DED is substantial on an individual in terms of quality of life, work productivity and vision as well as psychological and physical impact of pain. According to the TFOS DEWS II Epidemiological report [2], meta-analysis of published prevalence data estimated the impact of age and sex where global mapping of prevalence was undertaken. The prevalence of DED ranged from 5 to 50%. Women had a higher prevalence of DED than men. Studies performed in South East Asia [3-7] these reports showed the highest prevalence rates of symptomatic DED, ranging from 20.0 to 52.4%. Studies in Spain and USA showed a prevalence of 18.4% [8] and 14.5% [9], respectively.

The study definition used in both the studies were:

(1) frequency of symptoms, having at least one of the following symptoms of dry eye such as foreign body sensation, dryness, irritation, itching, or burning [10]

(2) self-reported diagnosis by agreeing with a sentence that describes dry eye that includes several symptoms

(3) using a cut-off value of the total score of the 12 item Ocular Surface Disease Index (OSDI) symptom questionnaire.

Majority of studies [4,7-9,11-13] reported a significantly higher prevalence in women compared to men, ranging from 1.33 to 1.74 times higher. Despite the difficulty of comparing studies directly because of their heterogeneity,

symptomatic DED is generally more common in women than men and more common in Asian than Caucasian populations.

The pathogenesis of dry eye disease [14] was attributed to the tear hyperosmolarity which was considered to be the triggering factor for a cascade of signalling events that activate epithelial Map Kinase (MAPK) and Nuclear factor kappa B (NFKB) which leads to the release of inflammatory mediators like interleukin 1, 17, interferon gamma, tumor necrosis factor alpha and matrix metaloproteases, These inflammatory cells causes goblet cells and glycocalyx mucin loss and epithelial damage. This is the root cause behind punctate epitheliopathy in dry eye disease and tear film instability contributing to early tear breakup time. This creates a vicious cycle where this tear film instability contributes further to tear hyperosmolarity and lead to ocular surface damage. However, in a study done by Kwon et al [17], their findings moved the current paradigm that focuses on T-cell mediated inflammation as central to the pathophysiology of DED to also include autoimmune inflammation that is driven by post-translational modifications in self-proteins (citrullination) and autoantibodies (ACPAs). Their findings pointed to citrullinated proteins on the ocular surface as the self-antigens driving autoimmune-based inflammation in DED. They also suggested that neutrophils may play a more prominent role in pathophysiology of DED than has been previously recognized. Citrullinated proteins stimulate the production of autoantibodies (ACPAs) that can not only cause ocular surface disease by a variety of mechanisms, but also stimulate formation of NETs, thus creating a self-perpetuating cycle of chronic inflammation on the ocular surface. Neutrophil extracellular traps (NETs) are webs of chromatin and proteins extruded from neutrophils during the process of NETosis. Although NETs are part of the innate immune defence, they can cause chronic inflammatory diseases. NETs are present on the ocular surface of patients

with severe tear-deficient DED subtypes (Sjögren's syndrome, ocular GVHD, non-Sjögren's DED, and ocular cicatricial pemphigoid).

Pathways involved in the current concept of pathology of dry eye disease detail involvement of naïve neutrophils egress from circulation to reach the ocular surface [17]. On the ocular surface, these neutrophils get activated and expresss FcγRI. Activated neutrophils form neutrophilic extracellular traps (NETosis). NETs release NET-associated proteins (e.g., LL-37, MPO and NE) that cause ocular surface inflammation, and PAD4 enzymes that citrullinate proteins in ocular surface cells (e.g. cit-histones in neutrophils). NETs accumulate on the ocular surface of DED patients either because of increased formation (due to hyperosmolarity) and/or reduced clearance (due to tear deficiency and consequent nuclease deficiency). Then citrullinated proteins are recognized by B cells and immune processing occurs with T cells. Then B cells differentiate to Plasma cells that secrete ACPAs. ACPAs form immune complexes with citrullinated autoantigens (ACPA-IC) on the ocular surface. ACPA-IC binds to FcγRI expressed on dendritic cells and neutrophils and lead to secretion of proinflammatory and nociceptive cytokines. ACPA-IC interacts with complement system to generate inflammatory mediators. ACPA-IC stimulates neutrophils to promote NETosis, thus creating a vicious cycle of chronic inflammation on the ocular surface.

MATERIALS AND METHODS

The study was a prospective longitudinal interventional open label comparative study conducted in Dr Rajendra Prasad Centre for Ophthalmic Sciences, AIIMS, New Delhi between the time period of April 2021 to July 2022. Chronic dry eye disease patients of moderate to severe grade were recruited with a minimum sample size of 30 patients in Cases and Control and each evaluated over a period of 6 months and as applicable. Patients with

>18 years age, with Tear break up time <7 seconds, Schirmer test ≤9 mm/ 5 minutes, Ocular surface disease index (OSDI) score ≥13, National Eye Institute (NEI) corneal staining score >3, National Eye Institute (NEI) conjunctival staining score >3 were included in the study. Patients not consenting to participate in topical IgG therapy, or with active ocular infection, active allergic conjunctivitis, active intraocular inflammation (retinitis/ choroiditis/ uveitis), pregnant/ nursing/ lactating, drug/ alcohol dependence were excluded from the study. Informed consent taken from all study participants (patient information sheet and informed consent form. Institute ethics approval was taken: IEC number: **IECPG-710/23.12.2020,RT-28/27.01**, CTRI registration number: **REF/2020/11/038410.**

A minimum of 30 cases of dry eye disease were recruited as controls following the inclusion criteria. These patients were started on lubricants (carboxymethyl cellulose 0.5% and lubricant ointment at bedtime), topical steroids (prednisolone 1%/ fluorometholone 0.1%/ loteprednol 0.5%) therapy as required and topical immunomodulators (Cyclosporine A 0.1% eye drops/ Tacrolimus 0.03% eye ointment) twice daily. Also a minimum of 30 dry eye disease patients were recruited as cases who were on all the above-mentioned medications and were started on topical human immunoglobulin IgG 0.4% twice daily [Topical ocular surface immunoglobulin was constituted from under strict asepsis in the ocular pharmacology department from the commercially available human IgG IV formulation and stored at 2-8 ºC, protected from light].

The demographic details of the patient, diagnosis, and history including ocular complaints, systemic or ocular co-morbidities, treatment history, drug history recorded on a predesigned proforma. All patients underwent comprehensive ophthalmic examination at recruitment inclusive of the following: (i) Anterior segment evaluation – Comprehensive slit Lamp

biomicroscopic examination of anterior segment and cornea, fundus evaluation & intraocular pressure (IOP) and ocular adnexa. (ii) Clinical photography (iii) Dry eye disease severity level was assessed in accordance to TFOS DEWS dry eye disease severity level and National Institute of Health score (NIH score) with ocular surface evaluation tests: (i) Schirmer's I test [19], Tear-film breakup time (TBUT) [20] (ii) NEI Corneal & Conjunctival Staining Score [21] (iii) Ocular Surface Disease Index (OSDI) score (iv) Conjunctival Hyperemia Score [23] . Study characteristics were evaluated at time of recruitment into the study (baseline visit) & at follow-ups. All study participants were evaluated at time of recruitment (baseline visit) and followed up at month 3, 6 month following recruitment and thereafter as applicable. Data of all study participants were entered into predesigned proforma. In the event of any worsening of signs and symptoms, ocular surface immunoglobulin was stopped and sent for culture sensitivity test.

Results:

71 eyes of 36 patients were recruited in cases group and 64 eyes of 32 patients were recruited in control group. In cases group, 47 eyes completed 3 month follow up, 53 eyes completed 6 month follow up and 33 eyes completed 12 months follow up, 12 eyes were lost to follow up. In control group, 40 eyes completed 6 month follow up and 20 eyes were lost to follow up.

There were 18 (50%) males and 18 (50%) females in Cases group and 19 (59%) males and 13 (41%) females in Control group. The mean age of presentation of the study subjects were 39 ± 11.80 years (21-63 years) and 40 ± 11.53 years (22-65 years) in Cases and Control group respectively. Mean age of males and females were 39.63 ±13.81 years (22-63 years) and 38.36 ±9.92 (26-56 years) in Cases and 43.19 ±11.63 years (23-63 years) and 36.5 ±10.98 years (22-55 years) in Control group respectively.

The etiological diagnosis of cases and control groups are described in Figure 1a and 1b and table 1. Details of study parameters in cases and control groups are elaborated in table 2.

A difference in score of more than 12.5 of OSDI score was considered to be significant, as this change from baseline indicates improvement by at least one category in half of the answered questions [22]. OSDI questionnaire noted significant difference (table 3, figure 2A) in 18 eyes (33.96%) at 6 months follow up in Cases and in 4 eyes (10%) for Control group. Statistically significant improvement was noted at 3 month follow up in study participants receiving topical immunoglobulin (p=0.0006) which sustained for 6 and 12 months. OSDI score was also statistically significant in Control group at 6 months follow up (p=0.0057). An improvement of Schirmer's I test value of >5mm of wetting at 5 min was considered as responders. In the cases group, 25 eyes (47.17%) treated with ocular surface immunoglobulin showed significant improvement at 6 months. In the control group 10 eyes (25%) showed significant improvement at 6 months treated with conventional therapy. The improvement noted in cases was significant at 3 month follow up (p=<0.0001) which sustained with the use of ocular surface immunoglobulin. Schirmer's score was not statistically significant at 6 month follow up in Control group (p= 0.0627). An improvement of >5 seconds of TBUT was considered as responders. 20 eyes (37.74%) in cases group, receiving topical adjunct immunoglobulin showed significant improvement at 6 months follow up. In control group, at 6 months follow up, 4 eyes (11.11%) showed significant improvement treated with conventional therapy. The improvement in the TBUT score was significant (<0.001) at 6 months follow up for both Cases

and Control groups which significantly improved at 12 months follow up for subjects receiving topical immunoglobulin and sustained with continued use

of the same. A decrease of NEI score 5 was considered as responders. 12 eyes (22.64%) showed clinical response in conjunctival staining score at 6 months follow up with ocular surface immunoglobulin whereas none of the eyes showed clinical response at 6 months follow up for patients receiving standard dry eye disease treatment. The clinical improvement was significant at 3, 6, 12 months follow up with ocular surface immunoglobulin treatment (p=0.0265/ <0.0001/ <0.0004) whereas non-significant in Control group at 6 months follow up (p=0.1779). In cases group, 10 eyes (18.87%) showed clinical response in the corneal staining score at 6 months follow up for subjects receiving topical immunoglobulin therapy. However only 3 eyes (7.5%) showed clinical improvement at 6 months follow up who did not receive the same. The improvement in Cases was statistically significant from 3 months (p=0.0001) follow up onwards. No significant improvement was seen in the control group at 6 months follow up (p=0.225). At the time of recruitment (n=71), the severity of conjunctival hyperemia in Cases was grade 4 in 20 eyes (28.17%), grade 3 in 21 eyes (29.58%), grade 2 in 26 eyes (36.62%) and grade 1 in 4 eyes (5.63%). However, a combined total of 20 eyes had grade 4 or grade 3 severity conjunctival hyperemia after 3 months (n=47) of adjunct topical immunoglobulin, which changed to 12 eyes (22.64%) and 6 eyes (18.18%) at the end of 6 months (n=53) and 12 months (n=33) follow up respectively. The hyperemia severity in Control group at recruitment (n=64) was grade 3 in 24 eyes (37.5%), grade 2 in 28 eyes (43.75%) and grade 1 in 8 eyes (12.5%). On continuing conventional therapy only for 6 months (n=40), 10 eyes (25%) had grade 3 hyperemia and 10 eyes had grade 2 hyperemia (25%). There was a significant decrease in conjunctival hyperemia in both Cases and Control groups over 6 months follow up. At the time of recruitment (n=71) in Cases, TFOS DEWS II score in 31 eyes (43.66%) were Level 4, 20 eyes (28.17%) were level 3, 14 eyes

(19.72%) were level 2, 6 eyes (8.45%) were level 1. After 3 months of adjunct topical immunoglobulin (n=47), 14 eyes had TFOS DEWS II score of level 4 (29.79%), 7 eyes at level 3 (14.89%), 10 eyes at level 2 (21.28%), 16 eyes at level 1 (34.04%). The improvement was sustained and continued similarly over 6 months and 12 months follow up. In the control group at baseline (n=64), 16 eyes (25%) had level 4 TFOS DEWS II score, 27 eyes (42%) had level 3 and 21 eyes (32.81%) had level 2 scores. On 6 months of follow up, 10 eyes (25%) had level 4 severity, 12 eyes (30%) were level 3, 8 eyes (20%) were level 2, 10 eyes were level 1 (25%). There was a significant improvement of TFOS DEWS II score in both the Cases and Control group at 6 months follow up.

The mean change in all ocular surface parameters in cases and control groups is tabulated in table 4. The median change in all ocular surface parameters between cases and control was compared over a 6 month follow up period (table 5). All the ocular surface parameters showed a statistically significant improvement in the cases as compared to the control group (Figure 3A and 3B).

DISCUSSION

In our study, the median age of population in cases group on topical adjunct immunoglobulin was 35.5 and 38.5 in control group. There was no significant difference in the age group between cases and control (p=0.512) in our study. There was an equal distribution of males to females in the Cases (1:1) group and a male preponderance (59%) in the Control group. Ocular GVHD patients (33%) formed the majority in Cases group receiving topical adjunct immunoglobulin followed by autoimmune DED (25%), MGD (14%), SJS (14%) and blepharokeratoconjunctivitis (6%). Whereas autoimmune DED formed the majority (47%) in control group followed by MGD (23%), SJS (13%), blepharokeratoconjunctivitis (7%). In our study, the baseline

OSDI score in cases and controls showed no significant difference between the groups. The mean OSDI score decreased in eyes on adjunct topical immunoglobulin from 72.62±14.83 at baseline to 68.04 ±13.35 at M3 follow up (p=0.0006), 57.27±17.08 at M6 follow up (p<0.0001) and to 57.53 ±14.13 at M12 follow up (p<0.0001). The mean OSDI score also decreased significantly in controls from 70.52±11.00 to 65.66 ±15.38 at M6 follow up (p=0.0057). The reduction in OSDI score in our study was significantly greater at 6 months follow up in cases group (-13.68 ±14.41; p=0.0002) as compared to control group (-3.84±7.84 units). DED severity level assessed by TFOS DEWS II score also showed significant reduction from 3.07 ±0.99 to 2.26 ±1.11 at 6 months follow up (p<0.0001) in cases group and from 2.95 ± 0.77 to 2.44 ± 1.13 at 6 month follow up (p=0.0005) in control group. The reduction in TFOS DEWS II score was significantly greater in Cases (-0.83 units; p=0.0227) as compared to control group (-0.44 units). This study noted a significant improvement in TBUT score over the follow up period in cases from 3.56 ±3.11 seconds to 7.02 ±3.39 seconds (p<0.0001) and control (p=0.0001) groups from 3.43 ± 2.14 seconds to 5.14 ± 2.39 seconds, both at 6 months follow up. Significantly greater improvement was seen in cases (+3.55 seconds; p=0.002) than control group (+1.56 seconds). The baseline Schirmer's I score in cases and control were comparable (p=0.682). The improvement in the Schirmer's I score was significant in only cases who received topical immunoglobulin therapy (+6.02±6.34 mm at 6 months; p=<0.0001) but not in control group (p=0.0627). The corneal staining score decreased from 6.20 units to 4.15 units in cases group over 6 months follow up (p<0.0001) but showed no statistically significant improvement in control group from 6.12 units to 5.36 units (p=0.225). The conjunctival staining score was unchanged in the Vehicle group [17] (2 units). Though it improved marginally from 4 units to 2 units in OSIG group at week 8 follow

up, statistically significant improvement was not noted (p=0.1663). The median conjunctival staining score of cases reduced from 5 units to 3 units over 3 months (p=0.0265). But it remained unchanged in the control group (p=0.1779). The median baseline conjunctival hyperemia had a significant difference at baseline (p=0.02) between cases (3 units) and control (2 units) groups in our study. There was an improvement from 3 units to 2 units at 3 months follow up (p<0.0001) in cases group which sustained at 6 months follow up (p<0.0001) and improved further to 1 unit at 12 months follow up (p<0.0001). Significant improvement was noted in control group as well at 6 months follow up (p<0.0001). However, the reduction in conjunctival hyperemia was significantly greater in the cases group (-1 unit; p=0.0001) as compared to control group (0 units).

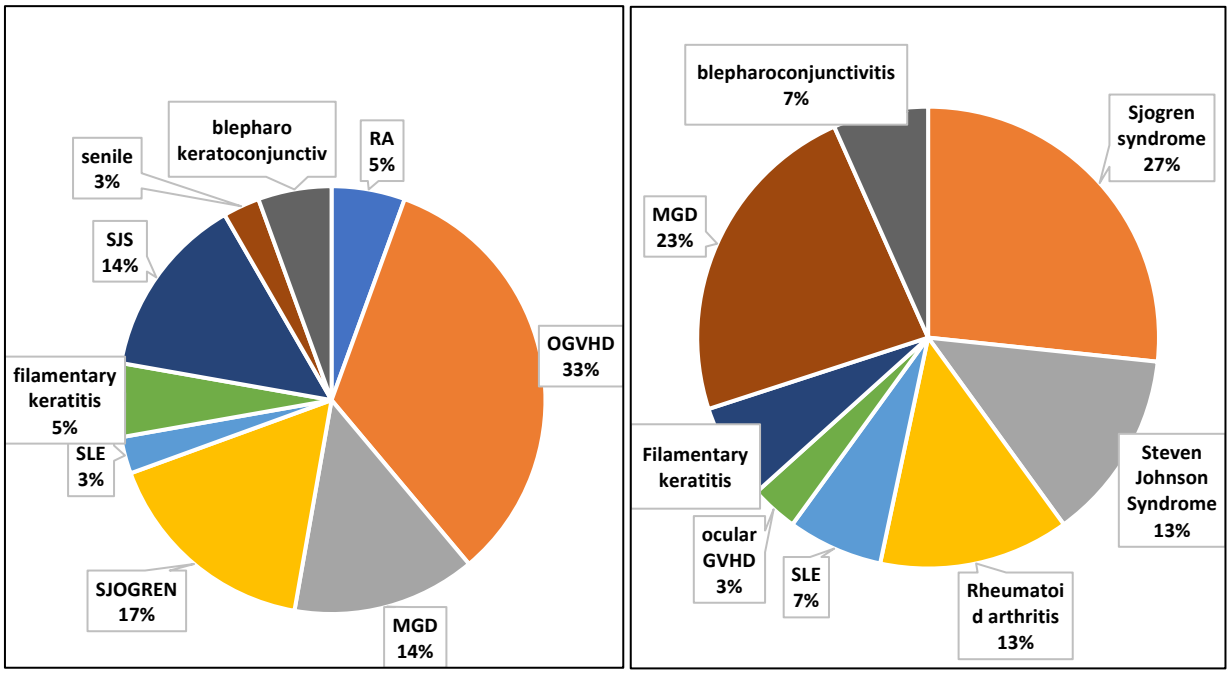
CONCLUSION

Statistically significant improvement in ocular surface evaluation parameters - TBUT, Schirmer, conjunctival & corneal staining score, hyperemia score, OSDI & TFOS DEWS 2 score noted with ocular surface immunoglobulin therapy was sustained over continued therapy. Minimum of 3-months use of immunoglobulin eye drops is advisable to achieve results as per our study observation. Success rate determined based on improvement in ocular surface evaluation was 75.76%, symptoms evaluation (OSDI) was 75.76%. Long-term adjunct ocular surface IgG therapy is effective in controlling ocular surface inflammation in refractory DED eyes.

REFERENCES

Table 1: Number of patients and etiology in Cases and Control groups

Diagnosis	Cases	Control
Ocular GVHD	12	1
Sjogren Syndrome	6	8
Steven Johnson Syndrome	5	4
Meibomian Gland Dysfunction	5	7
Filamentary Keratitis	2	2
Rheumatoid Arthritis	2	4
Blepharokeratoconjunctivitis	2	2
Systemic Lupus Erythematoses	1	2
Age Related	1	0



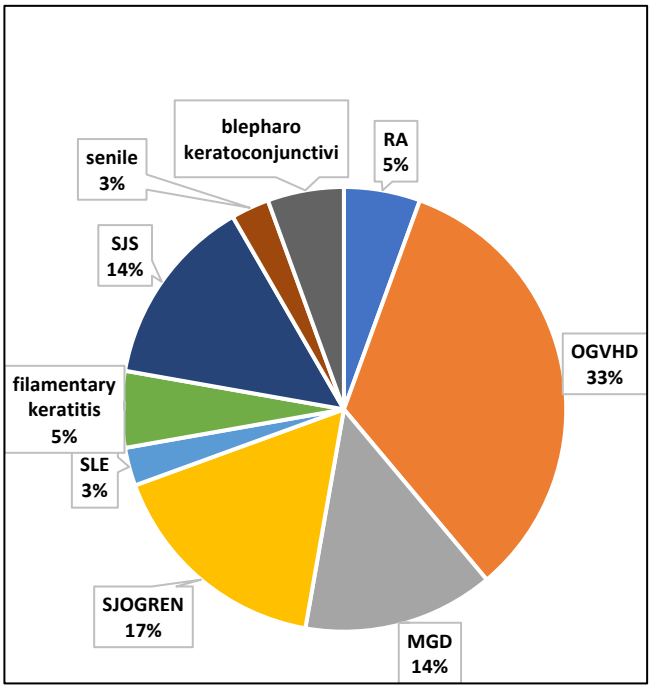


Figure 1a (left) and 1b (right): Clinical diagnosis of dry eye disease in Cases (left) and Control (right) groups

Study parameters (cases)	Baseline (n=71 eyes)	3 months (n=47 eyes)	6 months (n=53 eyes)	12 months (n=33 eyes)
DED severity (TFOS DEWS II score)	3.07 ±0.99	2.40 ±1.25	2.26 ±1.11	1.82 ±1.04
OSDI score	72.62±14.83	68.04±13.35	57.27±17.08	57.53±14.13
TBUT (sec)	3.56 ±3.11	5.36 ±2.94	7.02 ±3.39	8.21 ±3.11
Schirmer (mm)	8.55 ±8.20	13.43 ±9.49	14.81 ±8.98	18.88 ±7.34
Conjunctival staining score	6.37 ±4.43	4.32 ±3.14	4.06 ±4.12	3.15 ±3.83
Corneal staining score	6.20 ±3.57	4.42 ±3.49	4.15 ±3.65	3.03 ±3.49
Conjunctival hyperemia	2.80 ±0.92	2.02 ±1.13	1.81 ±1.11	1.49 ±1.09

Study parameters (control)	Baseline (n=64 eyes)	6 months (n=40 eyes)
DED severity (TFOS DEWS II score)	2.95 ± 0.77	2.44 ± 1.13
OSDI	70.52 ± 11.00	65.66 ±15.38
TBUT (sec)	3.43 ± 2.14	5.14 ± 2.39
Schirmer (mm)	7.02 ± 3.78	8.25 ± 5.53
Conjunctival staining score	6.57 ± 4.61	7.28 ± 5.31
Corneal staining score	6.12 ± 3.82	5.36 ± 3.44
Conjunctival hyperemia	2.27 ± 0.69	1.83 ± 0.85
Conjunctival hyperemia	2.27 ± 0.69	1.83 ± 0.85

Table 2: Mean values of study parameters of cases and controls during study period

Table 3: Study parameters of Cases and Controls

OSDI score (cases)	Median	p value*
Baseline (n=71 eyes)	72.9	
3 months (n= 47 eyes)	72.9	*0.0006
6 months (n=53 eyes)	62.5	**<0.0001
12 months (n= 33 eyes)	52.1	#<0.0001
OSDI score (control)	**Median**	**p value***
Baseline (n=64 eyes)	67.7	
6 months (n=40 eyes)	67.7	**0.0057

TBUT (cases)	Median	p value *
Baseline (n=71 eyes)	3	
3 months (n= 47 eyes)	5	*0.0001
6 months (n=53 eyes)	7	**<0.0001
12 months (n= 33 eyes)	8	#<0.0001
TBUT (control)	**Median**	**p value***
Baseline (n=64 eyes)	3	
6 months (n=40 eyes)	5	**<0.0001

Schirmer (cases)	Median	p value*
Baseline (n=71 eyes)	5	
3 months (n= 47 eyes)	10	*<0.0001
6 months (n=53 eyes)	12	**<0.0001
12 months (n= 33 eyes)	18	#<0.0001
Schirmer (control)	**Median**	**p value#**
Baseline (n=64 eyes)	7	
6 months (n=40 eyes)	8	**0.0627

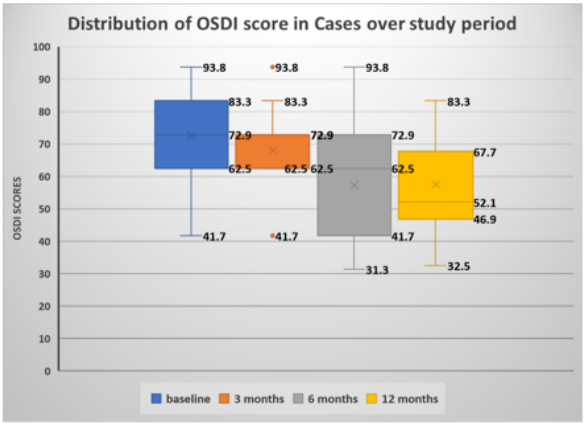
Conjunctival staining score (cases)	Median	p value*
Baseline (n=71 eyes)	5	
3 months (n= 47 eyes)	3	*0.0265
6 months (n=53 eyes)	3	**< 0.0001
12 months (n= 33 eyes)	2	#0.0004
Conjunctival staining score (control)	**Median**	**p value***
Baseline (n=64 eyes)	6	
6 months (n=40 eyes)	6	**0.1779

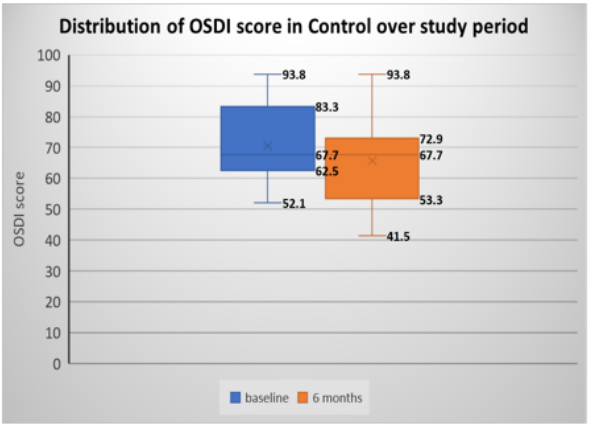
Corneal staining score (cases)	Median	p value*
Baseline (n=71 eyes)	6	
3 months (n= 47 eyes)	4	*0.0001
6 months (n=53 eyes)	4	**0.0001
12 months (n= 33 eyes)	3	#0.0001
Corneal staining score (control)	**Median**	**p value***
Baseline (n=64 eyes)	5.5	
6 months (n=40 eyes)	4	**0.225

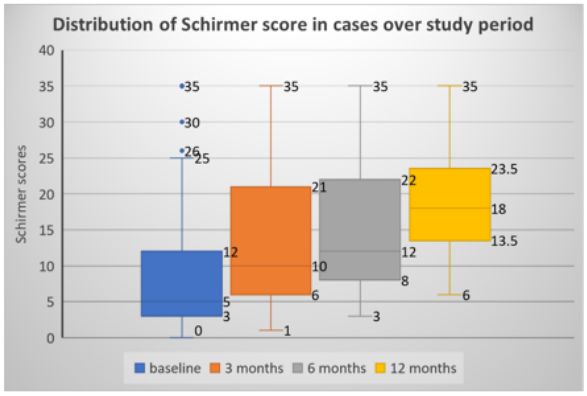
Conjunctival Hyperemia score (cases)	Median	p value *
Baseline (n=71 eyes)	3	
3 months (n= 47 eyes)	2	*< 0.0001
6 months (n=53 eyes)	2	**<0.0001
12 months (n= 33 eyes)	1	#<0.0001
Conjunctival hyperemia score (control)	**Median**	**p value #**
Baseline (n=64 eyes)	2	
6 months (n=40 eyes)	2	**<0.0001

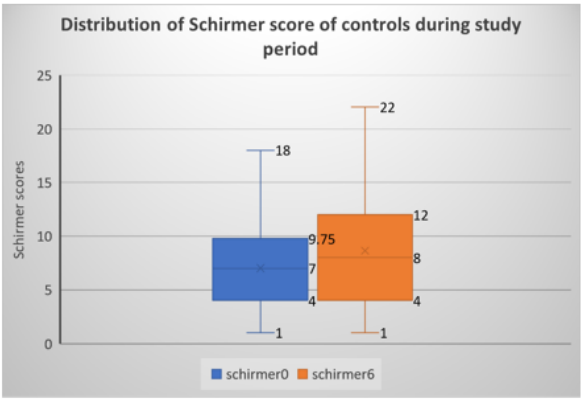
TFOS DEWS score (cases)	Median	p value *
Baseline (n=71 eyes)	3	
3 months (n= 47 eyes)	2	*<0.0001
6 months (n=53 eyes)	2	**<0.0001
12 months (n= 33 eyes)	1	#<0.0001
TFOS DEWS score (control)	**Median**	**p value#**
Baseline (n=64 eyes)	3	
6 months (n=40 eyes)	2.5	**0.0005

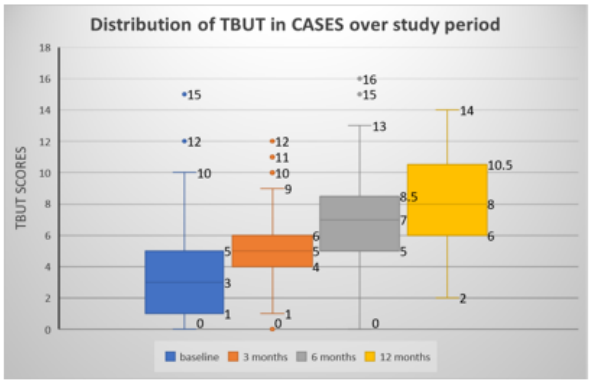
***Wilcoxon test #Paired sample T test**

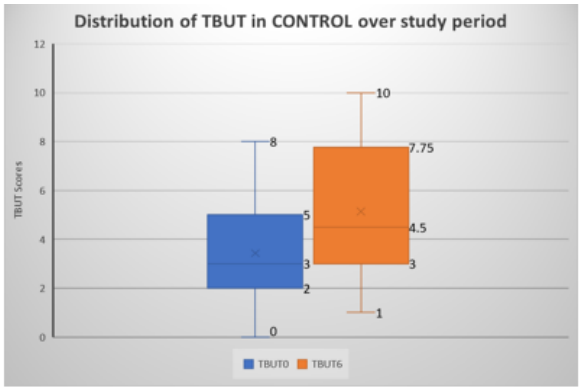


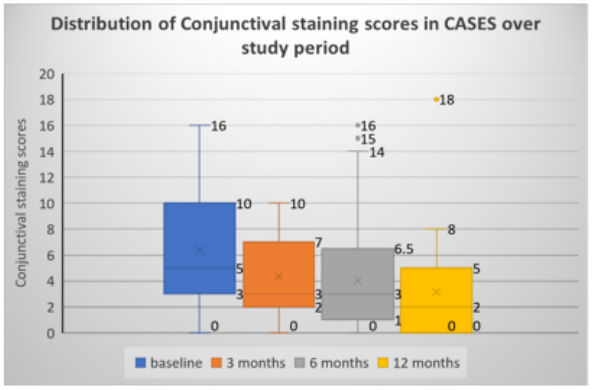












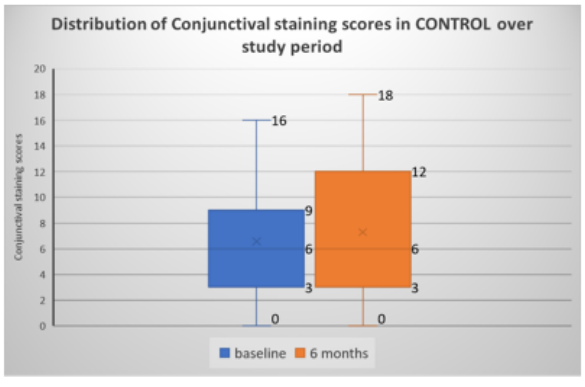


Figure 2A: Distribution of study parameters in cases and control groups

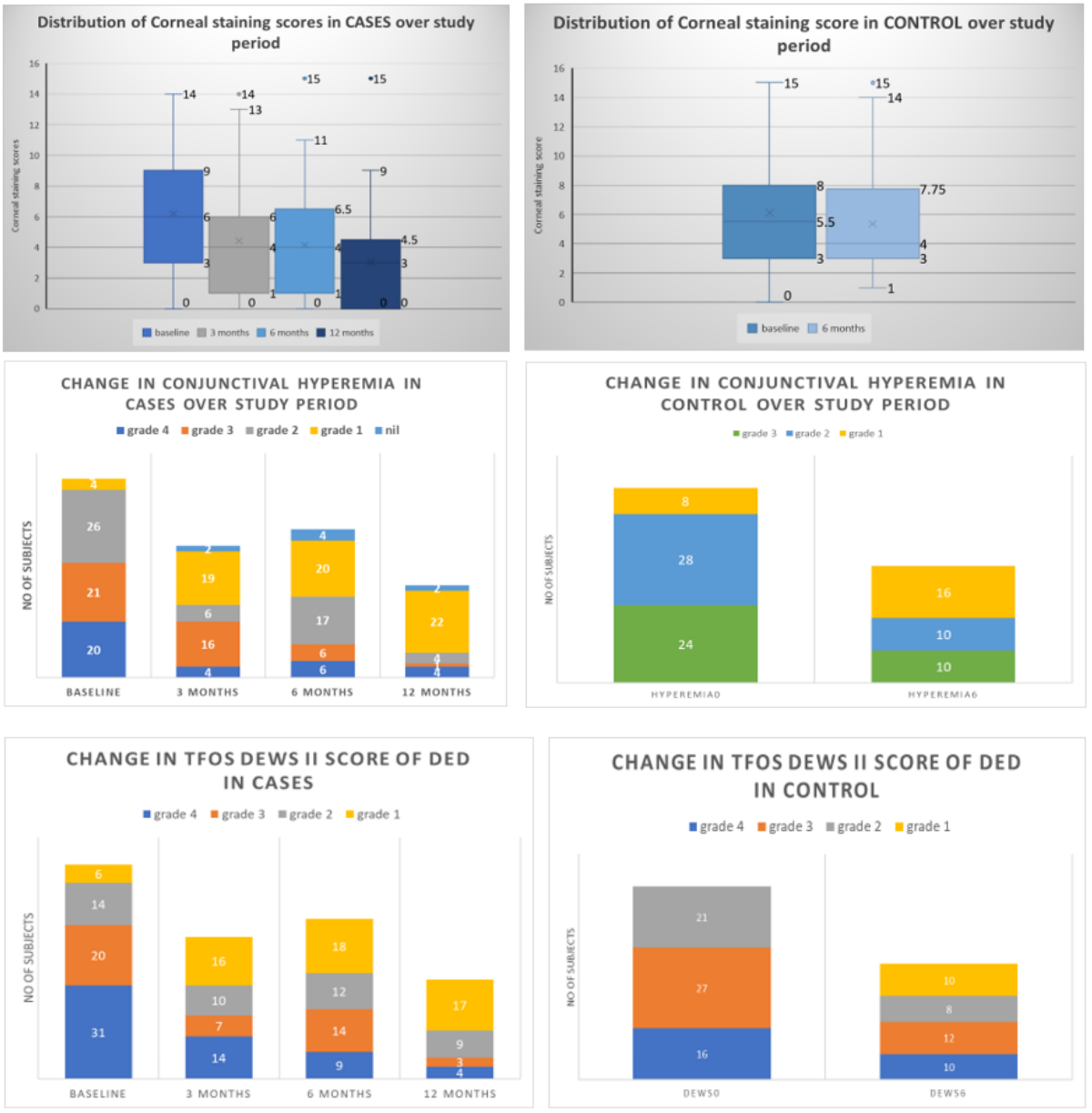


Figure 2B: Distribution of study parameters in cases and controls

Table 4: Mean change in parameters in cases and control groups

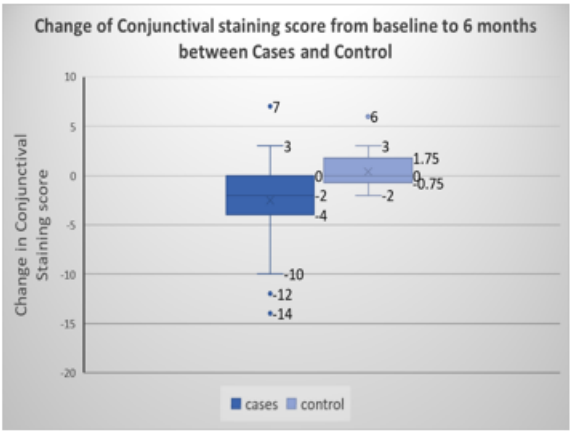
Mean change in parameters in Cases	Baseline to 3 months (n=47 eyes)	Baseline to 6 months (n=53 eyes)	Baseline to 12 months (n=33 eyes)
TFOS DEWS II score	-0.55 ±0.58	-0.83 ±0.85	-1.42 ±1.15
OSDI score	-3.99 ±7.38	-13.68 ±14.41	-17.27 ±17.23
TBUT (sec)	2.00 ±3.03	3.55 ±3.59	5.30 ±3.52
Schirmer's I test (mm)	+4.02 ±6.61	+6.02 ±6.34	+9.88 ±6.43
Conjunctival staining score	-1.49 ±4.20	-2.59 ±3.91	-3.91 ±5.75
Corneal staining score	-1.32 ±2.65	-1.68 ±2.74	-2.52 ±2.75
Conjunctival hyperemia score	-0.79 ±0.51	-1.00 ±0.62	-1.55 ±0.90

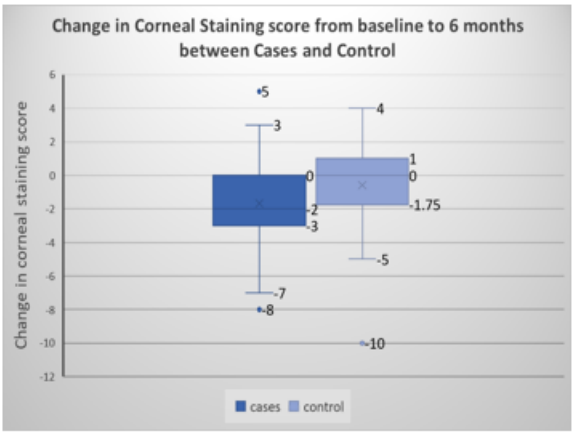
Mean change in parameters in controls	Baseline to 6 months (n=40 eyes)
TFOS DEWS II score	-0.44 ±0.70
OSDI score	-3.84 ±7.84
TBUT (sec)	+1.56 ±1.61
Schirmer's I test (mm)	+1.72 ±5.38
Conjunctival staining score	+0.39 ±1.62
Corneal staining score	-0.58 ±2.41
Conjunctival hyperemia score	-0.44 ±0.50

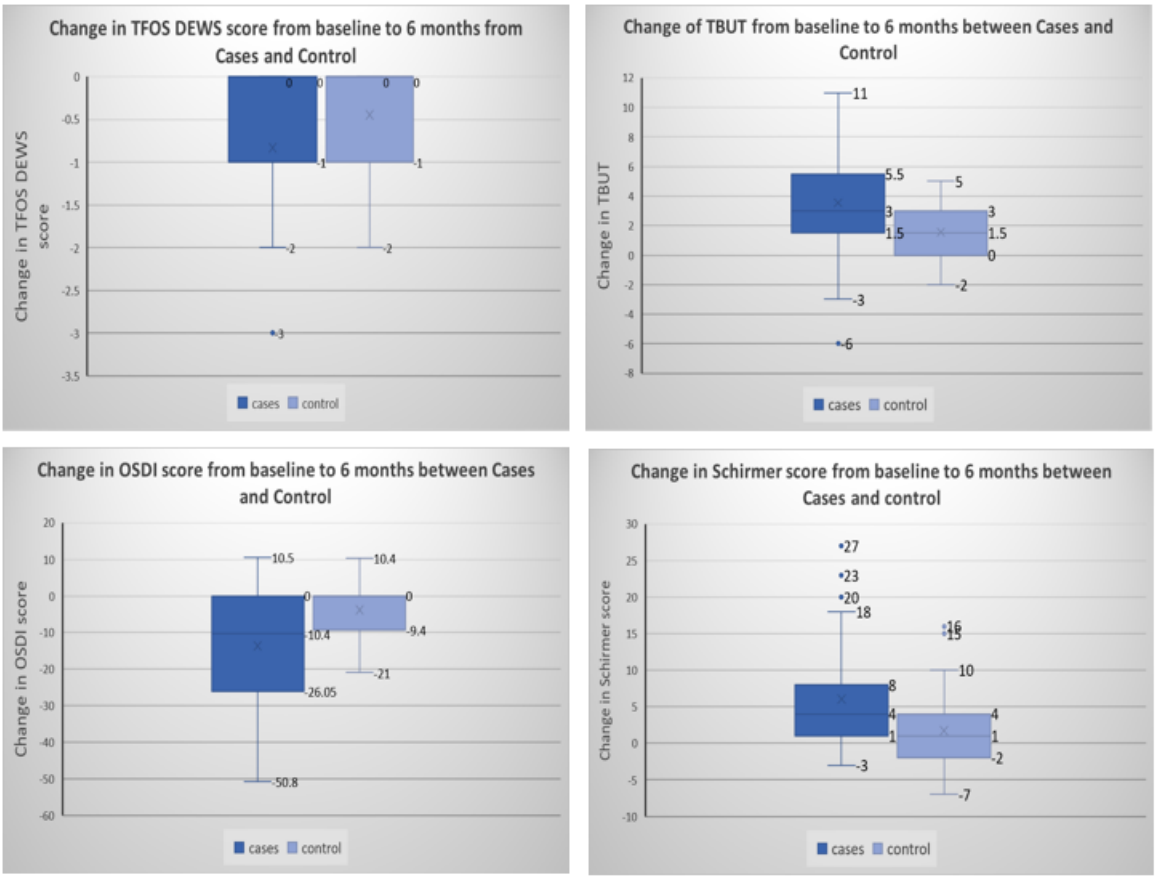
Table 5: Comparison of median change of parameters between cases and control over M-6 F

Parameters	Cases (n=53 eyes)	Controls (n=40 eyes)	p value*
TBUT (sec)	+3	+1.5	0.0020
Schirmer score (mm)	+4	+1	0.0006
Conjunctival staining score	-2.0	0.0	< 0.0001
Corneal staining score	-2.0	0.0	0.0136
Conjunctival hyperemia score	-1.0	0.0	0.0001
OSDI score	-10.4	0.0	0.0002
TFOS DEWS II score	-1	0.0	0.0227

Figure 6A: Comparison of study parameters in cases and controls from baseline to M6 FU







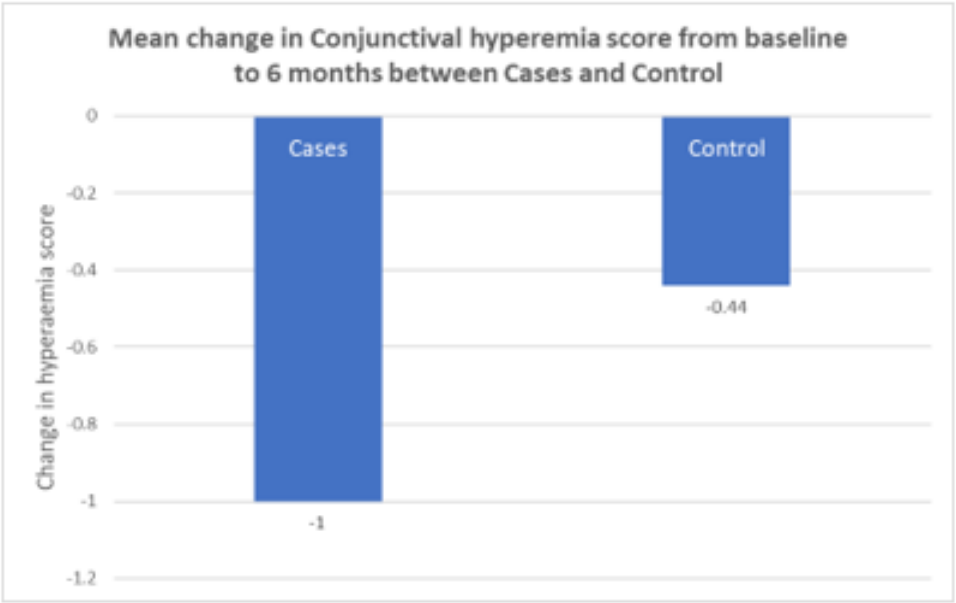


Figure 6B: Comparison of study parameters in cases and control from baseline to M6 FU

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AMNIOTIC MEMBRANE-UMBILICAL CORD (AM-UC) GRAFTS REFLECTING NEW RAYS TOWARDS GLAUCOMA SHUNT SURGERY.

INTRODUCTION

Glaucoma drainage devices remain an effective option for management of refractive glaucoma.

Our study aimed to determine the safety and efficacy of amnionic membrane-umbilical cord(AM-UC)graft in Glaucoma shunt surgery for reducing glaucoma shunt tube exposure.

METHOD

Hospital based prospective interventional study.50 eyes of 50 patients with refractory glaucoma underwent glaucoma shunt surgery using Ahmed valve. Tubes are inserted in anterior chamber(n= 45), pars plana (n= 5). Tubes were covered with AM-UC patch grafts. AS- OCT were used to asses the patch graft stability and host tissue integration with a focus on tube exposure, graft thinning and graft-related complication.

RESULT

The average age was 50 +/- 5 years. The mean follow-up 24+/-3 month.Tube exposure occurred in 1eye (2%) at 3 months. Sequential AS-OCT showed excellent host tissue integration. Early graft thinning <3 month occurred in 6

eyes(12%) and late thinning occurred in 2 eyes (4%). No evidence of graft rejection or infection was associated with AM-UC graft.

CONCLUSION

AM-UC grafts are well tolerated and high-tensile strength, low immunogenicity, and excellent host- tissue integration offer good tectonic support in glaucoma shunt surgery & also beneficial specially when limited cornea donor & eye banking services specially in COVID 19.

INTRODUCTION

Glaucoma drainage devices (GDDs) are used in the treatment of refractory glaucoma which is defined as uncontrolled IOP with progressive optic nerve damage despite maximum medical treatment combined with/without failed filtration surgery or with high risk of failure of filtration surgery.[1]Tube exposure is a potential sight-threatening postoperative complication seen in GDD implantation due to high risk of intraocular infection.[2-5]Long scleral tunnelling[6], scleral flaps[7], Tenon advancement[8] and allogenic patch grafts[9-13] such as sclera, pericardium, and cornea are being used to reduce the risk of tube exposure. However, these grafts are prone to progressive thinning and silent melt. [5,14,15]

Recent studies have shown that amniotic membrane- umbilical cord grafts (AM-UC)provide good tectonic support and avert immune-related graft thinning and melting. It has been speculated that AM-UC promotes good host-tissue integration and increases graft survival.[16] In this study we aim to determine the safety and efficacy of AM –UC graft in glaucoma shunt surgery for reducing glaucoma shunt tube exposure.

METHODS

This is a prospective, interventional, institution-based study carried out at a tertiary referral hospital in East India. This study was approved by the

Institutional Review Board and Ethics Committee. All study procedures confirmed to the tenets of the Declaration of Helsinki for research involving human subjects. Informed consent (written) was obtained from all patients participating in the study.

Fifty patients (50 eyes) with history of refractory glaucoma were included in the study. A detailed medical and ocular history was taken. A complete ophthalmic examination was conducted for all patients at baseline one week before the study. Patients more than 18 years age who had uncontrolled glaucoma with or without previous conjunctival cutting surgery including prior failed trabeculectomy were included in the study. Patients with history of previous GDD surgery, chronic ocular inflammation, previous cyclodestructive procedure or vision less than light perception were excluded.

SURGICAL TECHNIQUE

Peribulbar anaesthesia was used in all the patients. All the patients included in the study were operated upon by a single surgeon while the post operative evaluation was done by two other surgeons who were blinded to the pre-operative and intraoperative events. Priming of Ahmed Glaucoma valve was performed to check the integrity and patency of the valve by injecting 1cc of balanced salt solution with 26G cannula.A fornix-based conjunctival flap was created in the supero-temporal quadrant between two adjacent recti muscles.The implant was sutured to the sclera 8-10mm from the limbus with 9-0 nylon. The tube was inserted either in the anterior chamber or through pars plana in vitreous cavity in patients with history of previous vitrectomy. For insertion into the vitreous cavity, a pars plana clip was used to secure the tube to the sclera with a 9-0 or 10-0 nylon suture. The drainage tube was trimmed to permit 2-3mm insertion in the anterior chamber with a bevelled cut at 30 degrees. For anterior chamber insertion, paracentesis was

performed and viscoelastic substance injected following which anterior chamber was entered 1-3mm posterior to the limbus with 22G needle parallel to plane of iris. The tube was entered through the needle tract with bevel facing the corneal endothelium. The drainage tube was covered with amniotic membrane-umbilical cord (AM-UC) graft (AmnioPlast THICK™) sutured to sclera by 10-0 nylon. AmnioPlast THICK™ is a sterilised, minimally processed, dehydrated super-thick human umbilical cord derived membrane allograft with a thickness of more than 100 microns.[22] Conjunctiva was then anchored to the limbus with 8-0 vicryl sutures and subconjunctival antibiotic with steroid was injected. (Figure1(b)and(c)) All anti-glaucoma medications were stopped from post-operative day 1 and patients were followed up regularly as mentioned before.

Postoperative Treatment and Follow-up

All patients were followed-up for postoperative visitson 1 day, 1 month, 3, 6, 12 and 18 months. Detailed clinical examination of anterior and posterior segment with IOP examination were conducted at each visit and anti-glaucoma drops were added if IOP>21 mm Hg was recorded. Graft was examined and complications like tube exposure, conjunctival erosion were noted. High-resolution spectral-domain AS-OCT (RTVue®, OptoVue, Inc., Fremont, CA or Cirrus, Zeiss Meditec, Dublin, CA) to assess patch graft thickness, stability and host-tissue integration was done at every visit. A series of four horizontal cut sections showing the round cut section of the tube were obtained, to ensure the cut sections were as perpendicular to the tube plane as possible. A line was then drawn from the apex of the tube to the surface of the conjunctiva (Figure 2B). The lowest of the 4 values was recorded as the thickness.

OUTCOME MEASURES

Outcome measures were assessed in a masked fashion by reviewing all preoperative and postoperative data including slit lamp examination, colour slit lamp photography and AS-OCT to monitor: (1) tube exposure; (2) tectonic integrity of the graft and the development of asymptomatic graft thinning; (3) other complications such as wound leak, leaking bleb, shallow or flat anterior chamber, hyphema, hypotony, choroidal effusion, motility restriction, uncontrolled intraocular pressure (IOP) and reoperation.

STATISTICAL METHODS

All statistical analyses were performed using the SPSS21.0. For continuous variables, t-test or paired t-test was performed for data with normal distribution, while a corresponding non-parametric test was used for abnormal distribution data. For categorical variables, Chi-square test or Fisher's exact test was used. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 50 eyes of 50 patients (38 males, 12 females, aged 42±13 years) received Ahmed Glaucoma Valve implantation. GDD were placed in the superior-temporal quadrant and tubes were inserted in the anterior chamber (n=45) or pars plana (n=5) for patients with history of pars plana vitrectomy. Thetubes were covered with AM-UC for all patients. The mean number of previous intraocular surgeries were 1.5±0.5, which included phacoemulsification, trabeculectomy and pars plana vitrectomy. Baseline clinical characteristics and demographic data are summarized in Table 1.

The mean preoperative IOP was 28.8±2.4 mmHg (range 24-31). The mean postoperative IOP at 1 month was 12.4±5.7mmHg, at 3 months was 14.2±6.5mmHg, at 6 months was 14±4.6 mmHg, at 1 year was 15.4±6.3 mmHg and at the last follow up at 18 months was 15.7±6.1 mmHg. There was

significant reduction of IOP at each follow up visit from preoperative value ($p<0.05$ at each visit). The mean number of preoperative glaucoma medications was 3.3±0.5 while at 18 months was 1.2±0.8 ($p=0.08$).

Sequential AS-OCT showed good host-tissue integration and mild graft thinning in AM-UC patch grafts.(Figure 1). Graft thickness at one-month was recorded and was compared to the following visits at three months, six months, 12 months and 18 months. The average graft thickness of AM-UC at one month was 400 ± 15µm, at three months was 340 ± 18 µm, six months was 300 ±18 µm, twelve months was 280 ± 17 µm and at final follow up at 18 months was 274 ± 15 µm (Figure 2). Early graft thinning, defined as >20% reduction of the graft thickness at 3-month, occurred in 6 eyes (12%) in AM-UC with an average thickness of 255±78 µm (range 182-324 µm) (Figure 3). Late thinning at 12-month continued in 2 eyes (4%) in AM-UC with an average thickness of 206±27 µm (range 179-233 µm) (Figure 4). In cases with progressive thinning/melting, the conjunctiva remained stable over the tube without erosion. Other postoperative complications not related to the graft material included persistent hypotony in 2 eyes, corneal oedema in 4 eyes and shallow AC with iridocorneal or tube touch in 2 eyes. The two patients who developed postoperative shallow anterior chamber with hypotony were managed with oral steroids and cycloplegic agents. Reforming the anterior chamber with viscoelastic substance was required in one patient.There was no evidence of graft rejection, severe inflammation or infection associated with the AM-UC patch graft. The postoperative complications are summarised in Table 2.

The AM-UC covered area was aesthetically appealing and the translucency of AM-UC allowed direct visualization of the underlying tube and permitted easy laser suture-lysis when needed to control early postoperative ocular hypertension. Tube exposure occurred in 1 eye (2%) in AM-UC group within

3 months after receiving Ahmed valve implant. The eye with tube exposure underwent surgical revision to cover the tube with a scleral patch graft.

DISCUSSION

Sheha et al[16] were the first to conduct a multicentre trial using AM-UC as a patch graft for GDD implants and compared the results to that seen in pericardium patch grafts. It was hypothesized by Sheha et al[16] that the AM-UC graft probably has an unknown biological activity to promote host-tissue integration and increase graft survival. Our study confirms the findings reported by Sheha et al.[16] AM-UC has long-term stability and efficacy in reducing tube exposure and graft thinning. The AS-OCT findings suggest that AM-UC not only provides strong tectonic support but can also avert immune-related graft melting due to anti-immunogenic properties. It has improved host-tissue integration and is translucent, thus improving cosmesis. The AM-UC patch grafts are particularly beneficial in times of limited eye banking services as was the case during COVID 19 pandemic.

In this study, tube exposure rate of AM-UC graft was 2%, which was similar to that found in the study by Sheha et al. [16] The incidence and timing of tube exposure were also comparable to other studies.[13-15,17,18] A large meta-analysis of 38 studies by Stewart WC et al [5]also reported a tube exposure rate of 2.0±2.6% in GDD implantation with an average follow-up period of 26±3 months. However, our study had a much shorter follow up of 18 months. In our study, only one patient hadtube exposure which occurred within 2-6 months and was not preceded by progressive graft thinning. A longer follow-up period in our study may have produced different results. The eye with tube exposure had the tube inserted in the anterior chamber at the superior temporal quadrant. It has been suggested by previous studies that mechanical rubbing mechanism as previously suggested.[15,19,20]Anand A et al[17]reported that inadequate healthy conjunctival covering was a direct

cause of early patch graft exposure and melting and also suggested that complete conjunctival covering was also important as it was a source of native cells that promotes host-tissue integration until the patch graft achieves full tectonic strength. Chaku M et al[20] reported that history of previous and/or combined surgeries are associated with conjunctival dehiscence or scarring leading to tube exposure.

AM-UC has one of the lowest rates of graft thinning among all patch grafts that have been used for primary tube coverage and measured both clinically and with AS-OCT. [12,15,16,21]A 26% incidence of patch graft melting and/or thinning was reported by Smith et al[15]where three patch grafts, namely pericardium, sclera, and dura mater were retrospectively compared. Raviv et al[12] reported an 11.4% rate of progressive thinning/melting in pericardium within 10 months. In these studies, as the graft material was opaque, progressive thinning and or melting were determined clinically by the disappearance of the graft so thatthe tube was clearly visible beneath the intact conjunctiva. Recently gamma-irradiated sterile cornea patch grafts have become a popular choice for tube covering. However, De Luna et al[21] have recently reported a high rate of progressive corneal graft thinning over an average period of 1.7 years. They reported complete melting of the corneal patch graft by AS-OCT in 16.6% of cases.

Therefore, AS-OCT was selected for this study due to several advantages, including the higher resolution and non-contact scanning in the setting position. In other words, AS-OCT was better in terms of patient safety, comfort and compliance in the clinic setting. Limitation of this study is that no comparison tissue was used. This study only allows conclusions about the progressive of AM-UC and doesnot conclude its effectiveness with respect to the other patch graft tissues available under similar circumstances. Our study had a short follow up period of 18 months. Progressive graft thinning

has been observed in 8 patients which suggests a longer follow up period is necessary to truly confirm the effectiveness of AM-UC in long term.

CONCLUSION

AM-UC grafts have high tensile strength, low immunogenicity with excellent host tissue integration properties. These properties have improved their long-time survival with less chances of graft thinning.No evidence of graft rejection, severe inflammation or infection was associated with AM-UC patch graft.

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TABLES:

TABLE 1: Baseline characteristics:

Age (years) Mean + S.D. Range	42 30-50
Gender Male: Female	38:12
Eye Right : Left	30:20
Lens status	
Phakic	14
Pseudophakic	34
Aphakic	2
Type of Glaucoma	
Open angle	34
Angle closure	6
Others	10
Number of previous surgery	1.5 $\pm$0.5
Location of the tube insertion	
Anterior Chamber	45
Pars Plana	5

TABLE 2: Postoperative complications:

COMPLICATION	NUMBER (%)
Early graft thinning	6 (12%)
Late graft thinning	2 (4%)
Tube exposure	1 (2%)
Others (non-graft related)	8(16%)

FIGURES

FIGURE 1: Sequential AS-OCT images showing host tissue integration at (a)1 month, (b) 12 months

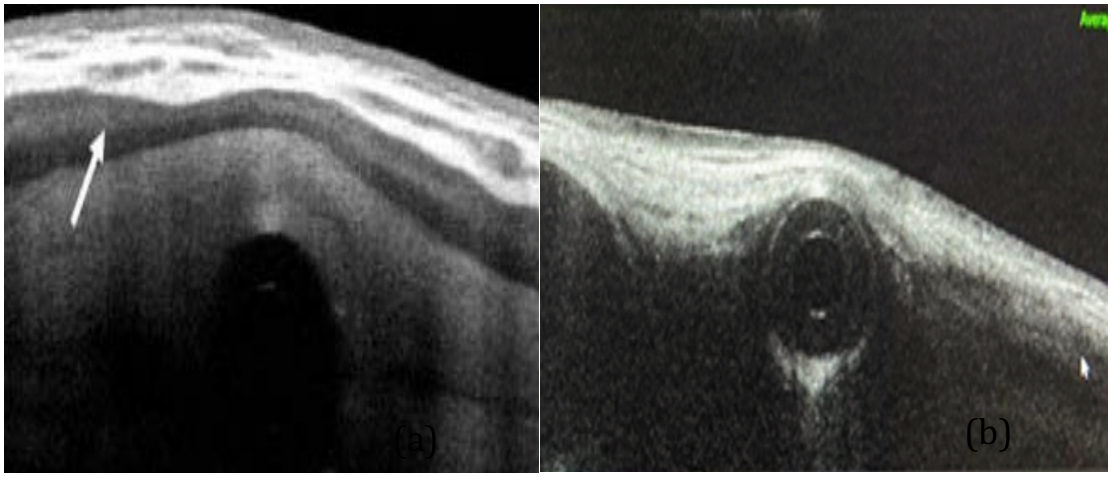


FIGURE 2:Average graft thickness at each postoperative visit:

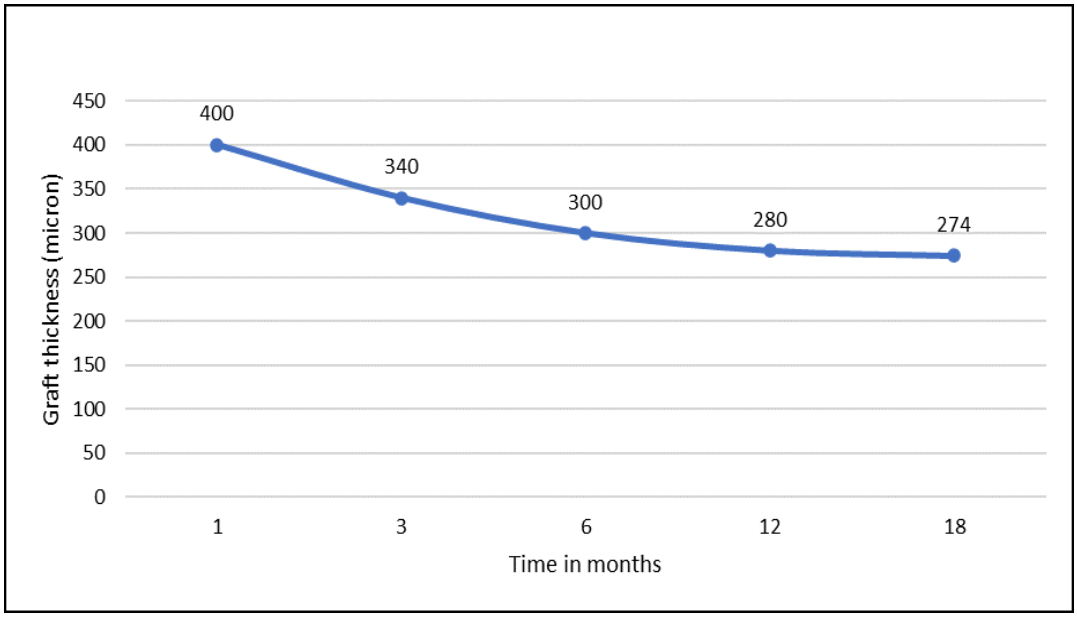


FIGURE 3: (a) Early graft thinning at 2 months, (b) Tube exposure

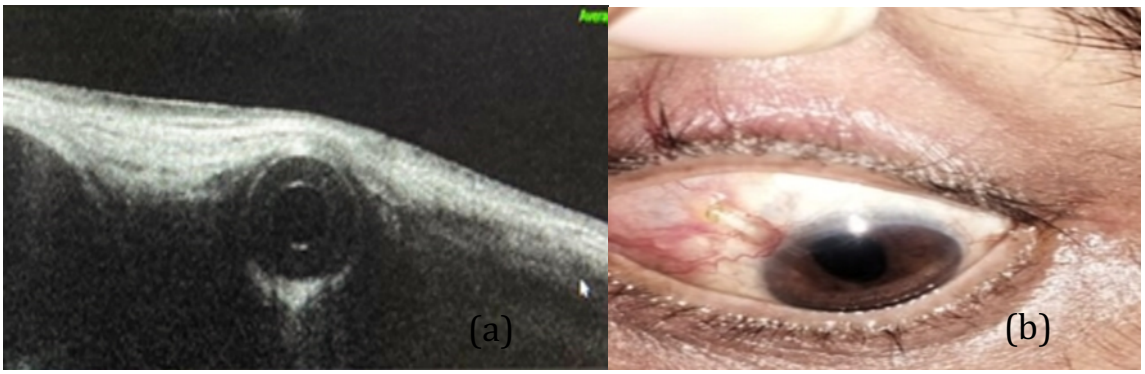
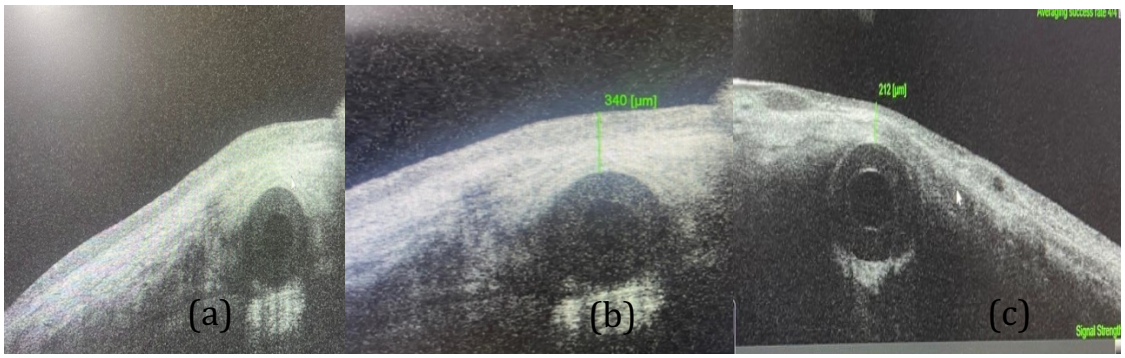


FIGURE 4: Late graft thinning (a) 1 month, (b) 6 months, (c) 12 months:



This paper was judged as the BEST PAPER of Glaucoma – II Session

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SHALLOW AC DEEP PROBLEMS: IZHV FOR ACUTE INTRAOPERATIVE AQUEOUS MISDIRECTION IN PHACOEMULSIFICATION

PURPOSE

To assess the outcome of Irido-Zonulo-Hyaloido-Vitrectomy (IZHV) as the treatment for acute intraoperative aqueous misdirection (AM).

METHODS

This is a retrospective case series of 7 consecutive patients who underwent IZHV as the treatment for acute intraoperative aqueous misdirection. AM was diagnosed as sudden shallowing of anterior chamber with markedly elevated intraocular pressures that did not respond to patient's, breathing, positioning, speculum adjustment and iridectomy, in the absence of suprachoroidal hemorrhage or effusion between April 2017 to August 2022 at a tertiary centre with a minimum follow of 1 month.

RESULTS

Five eyes had angle closure disease of which one of them had pseudoexfoliation, one eye had open angle glaucoma and one eye did not have glaucoma. 4 eyes were undergoing combined cataract and trabeculectomy. 4 eyes had aqueous misdirection during or after cortical aspiration and 2 eyes after creation of ostium suggesting as sudden

shallowing as a predisposing factor. IZHV was performed for all and resolution was achieved instantly. There was no recurrence in any of them postoperatively. Angle closure disease and preoperative high IOP were identified as the most common risk factors. Majority of the eyes had a BCVA of 20/80 or better and only one had poor vision which was attributable to vascular occlusion. In cases of combined surgery, IOP was under control in all the eyes, without the need for any medications in 2 eyes and the other 2 cases required topical anti-glaucoma medication. In cases who were underwent phacoemulsification alone, IOP was under control without any medication in one eye and 2 eyes with topical medication.

CONCLUSION

Our experience suggests IZHV can be an effective and safe solution for acute aqueous misdirection

INTRODUCTION

Acute intraoperative aqueous misdirection syndrome is a rare clinical condition characterized by sudden intraoperative shallowing of anterior chamber with marked increase in intraocular pressure during surgery in the absence of suprachoroidal effusion and hemorrhage. It is also known as infusion misdirection syndrome,[1] ciliary block, subcapsular fluid entrapment,[2] acute intraoperative rock-hard eye syndrome. To understand fluid misdirection having a good knowledge of the anatomy and physiology is important particularly the middle segment of the eye which includes ciliary body, lens, zonular diaphragm and the anterior vitreous. Aqueous produced by the ciliary processes goes in the conventional route other than that a part of which goes posteriorly to the vitreous cavity. The factors that maintain the equilibrium of aqueous flow are the proximity of ciliary processes to the vitreous body and the permeability of the hyaloid face. The

above factors get compromised in aqueous misdirection which causes accumulation of fluid in the posterior segment leading to increased positive pressure in the vitreous (vitreous expansion)[3] and forward displacement of iris lens diaphragm and flattening of anterior chamber. The initiating event is sudden decompression of the anterior chamber during surgery where the vitreous face might come forward abutting the ciliary processes which might cause the disproportionate amount of fluid to flow more posteriorly and it gets perpetuated by thickened hyaloid which decreases the permeability. Risk factors for the development of aqueous misdirection are angle closure glaucoma,[4] short axial length,[5] plateau iris,[6] zonular laxity, pseudoexfoliation,[1] preoperative high IOP,[7] large intumescent lens and use of pilocarpine preoperatively.

SURGICAL TECHNIQUE

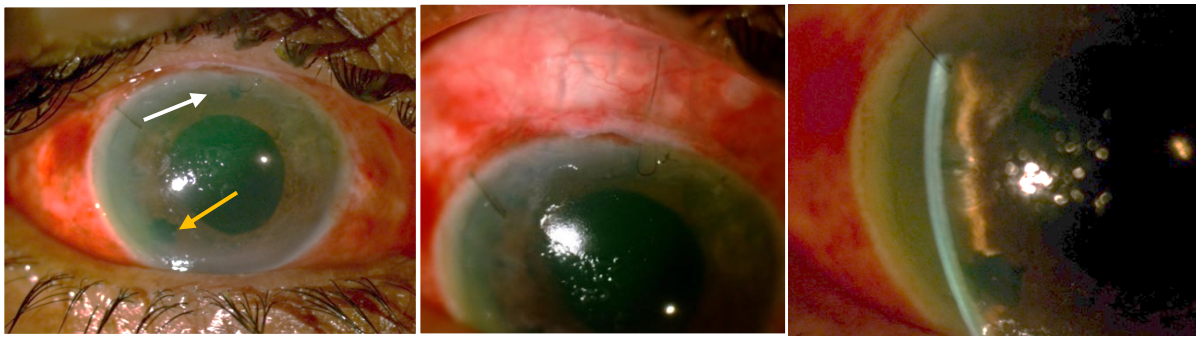
All surgeries were performed by glaucoma specialists under topical or local anesthesia. The diagnosis of acute intraoperative aqueous misdirection was made when there was sudden shallowing of anterior chamber with markedly elevated intraocular pressures and were sometimes accompanied by features including an inability to inject ophthalmic viscosurgical devices (OVDs), iris prolapse, spontaneous extrusion of OVD through the incisions and resistance to IOL implantation, in the absence of suprachoroidal hemorrhage or effusion. The causes of external globe compression (eg. tight speculum) were ruled out and we also ensured that the patient was breathing normally or no positive pressure was exerted by the patient. IZHV was performed through an anterior approach to decrease the posterior vitreous pressure. A peripheral iridectomy was performed with I/A Cut mode as we need to have sufficient vacuum to hold the iris, cut rate must be as low as possible to control the size of the peripheral iridectomy. Zonulo-hyaloido-vitrectomy was proceeded in Cut I/A mode (low vacuum, high cut

rate, no traction) through the iridectomy opening. While performing zonulectomy, the direction of the cutter should face towards the sclera to avoid damage to the capsule and the cutter should face anteriorly while performing vitrectomy as we do not want to injure the ciliary processes. Sustained deepening of anterior chamber is the end point of IZHV. Subconjunctival dexamethasone and atropine were given at the end of the procedure.

RESULTS

Our retrospective case series included 7 eyes of 7 subjects who underwent IZHV as the treatment for acute intraoperative aqueous misdirection between April 2017 to August 2022. Table 1 shows the baseline demographic data, preoperative, intraoperative and postoperative clinical findings of the patients. Amongst the 7 subjects 4 were females and 3 were males. Five eyes had angle closure disease [3 PACG, 1 PAC (PIS), PXFG with angle closure], one eye had open angle glaucoma and one eye did not have glaucoma. All the eyes with angle closure had undergone YAG peripheral iridotomy. 4 of 7 eyes were underwent combined cataract and trabeculectomy.

The time at which the intraoperative aqueous misdirection was noted was documented in 6 cases. 4 eyes had AM during or after cortical aspiration (in case 4, 5 aqueous misdirection was diagnosed after the withdrawal of I/A and in case 1,7 it was noted after the IOL placement. In 2 eyes (case 2,3) it was identified during the suturing of the scleral flap. Anterior vitrectomy was performed in case 7 as there was posterior capsular rupture with vitreous loss.



1a. 1b. 1c.

Figure 1. Slit lamp photograph of case 1 on postoperative day 1a Patent surgical iridectomy at 1 0’ clock(white arrow) and IZHV opening at 7 0’ clock(yellow arrow).b. Diffuse bleb with good bleb height c. Well-formed anterior chamber.

Anatomical success (well-formed anterior chamber) was achieved in all the cases. Intraocular pressure was under control without medications in 3 eyes and with medications in 4 eyes. One week postoperatively in case 3, there was shallowing of anterior chamber. Postoperatively, all the cases had achieved the BCVA of 20/80 and better, with an exception of case 4, where the BCVA was 20/100p as the patient developed branch retinal vein occlusion with macular edema. She was given intravitreal avastin injection and ozurdex implant due to persistent macular edema. There was no recurrence of aqueous misdirection in any of them except in case 3, which had shallow anterior chamber with borderline high IOP due to closure of IZHV opening with a membrane and hence YAG hyaloidotomy was performed which led to resolution of AM.

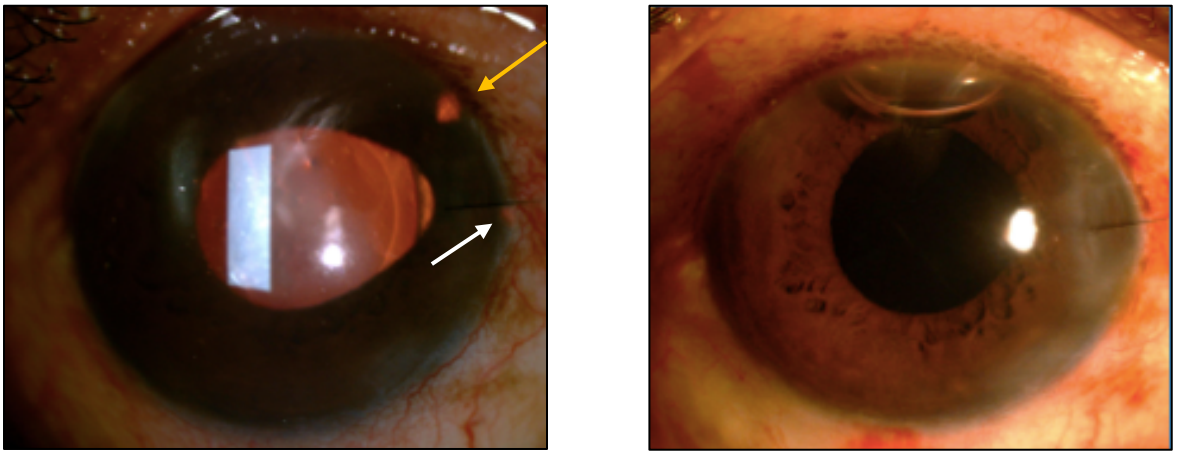


Figure 2 Slit lamp photograph(retroillumination) on the left shows IZHV opening at 2 0’ clock(yellow arrow), patent YAG peripheral iridotomy at 3 0’ clock (white arrow). Interrupted suture(10-0 nylon)at temporal phaco incision is seen on diffuse illumination on the left.

Table 1 Baseline characteristics

BASELINE CHARACTERISTICS												
Case	Surgery	Age[1]	Sex[2]	Eye[3]	Glauco Diagno	BCVA	LPI	IOP[5]	Meds	AL[6]	ACD[7]	LT[8]
1	Phaco-Trab	61	F	R	PACG	20/40	Yes	36	5	20.65	1.78	4.62
2	Phaco-Trab	52	F	R	PACG	20/60	Yes	33	1	22.18	NA	4.43
3	Phaco-Trab	70	M	R	PAC (PIS)	20/50p	Yes	19	5	22.9	2.27	4.67
4	Phaco	73	F	R	PACG	20/200	Yes	24	2	22.22	2.35	4.49
5	Phaco	64	M	L	POAG	20/100	Yes	18	2	28.64	3.07	4.83
6	SICS-Trab	66	M	R	PXFG4	CF@1m	Yes	25	3	23.14	1.82	4.01
7	Phaco	70	F	L	NA	20/50p	NA	14	0	22.99	2.81	4.57

1 Age in years; 2 M: Male, F: Female; 3: R: Right, L: Left; 4: With closed angles; 5: PI: Laser peripheral iridotomy; 6: Axial length (in mm); 7: Anterior chamber
depth (in mm); 8: Lens thickness (in mm)

Table 2 Outcomes at last follow-up

FINAL FOLLOW-UP								
Case	Surgery	Step at which intraoperative aqueo misdirection noted	Follow up[1]	IOP[2]	Visual acuity	No. of AGM	Additional procedures	Risk factors
1	Phaco-Trab	After IOL implantation	2.5	13	20/50	0	Nil	Preop high IOP, angle closure, use of pilocarpine
2	Phaco-Trab	Suturing the Scleral flap	2	14	20/80p	0	Nil	Preop high IOP, angle closure, Intraoperative cough
3	Phaco-Trab	Suturing the Scleral flap	30	19	20/20	4	Nd YAG Hyaloidotomy	Preop high IOP, angle closure, use of pilocarpine, plateau iris

4	Phaco	After withdrawal of I/A	15	13	20/100p	5	Intravitreal Anti-VEGF, Steroid3	Preop high IOP, angle closure
5	Phaco	After withdrawal of I/A	48	18	20/30	4	Nil	? Combined mechanism
6	SICS-Trab	Not mentioned	1	14	20/40p	4	Nil	Preop high IOP, angle closure, PXF
7	Phaco	After anterior vitrectomy and IOL placement	4	16	20/25p	0	Nil	Nil

1: In months; 2: in mm Hg; 3: For BRVO+ CME

PACG – Primary angle closure glaucoma, PAC – Primary angle closure, PIS – Plateau iris syndrome, PXFG- Pseudoexfoliation glaucoma, I/A – Irrigation and aspiration, BRVO – Branch retinal vein occlusion, CME – Cystoid macular edema, AV – Anterior vitrectomy

DISCUSSION

Acute intraoperative aqueous misdirection is probably under reported but might be experienced by many surgeons. The diagnosis and management of AM can be challenging. Aspiration of the retrolenticular fluid[3] with 23G needle by parsplana approach (transconjunctivally/ transclerally) or vitreous decompression using a small guage trocar/cannula vitrectomy cutter (23, 25 or 27 G).[4] The goal is to make a unicameral eye removing the

hyaloid barrier. Aspiration of fluid using a needle from the posterior segment might have a risk of engaging the vitreous causing traction and retinal tear formation. Small gauge trocar/ vitrectomy cutter is preferred as there would be negligible amount of traction. This entity of acute fluid misdirection syndrome in all practical purposes is similar to malignant glaucoma apart from the acute intraoperative presentation and hence we decided to treat with IZHV especially when there is no vitreoretinal set up.

Majority of eyes in our series had angle closure disease (5 out of 7 eyes, 71.4%) which was consistent with the literature.[8,9]All eyes with angle closure disease underwent YAG peripheral iridotomy. The risk factors for fluid misdirection are hyperopia, history of angle closure, plateau iris, pseudoexfoliation, preoperative high IOP, use of pilocarpine, coughing, intumescent cataract and coughing. Angle closure disease and preoperative high IOP are identified as the most common risk factors. One of the patients used pilocarpine, 1 had intraoperative cough and 1 had PXF.

AM usually occurs rapidly towards the end of irrigation/ aspiration(I/A) making the completion of I/A and implantation of intraocular lens difficult. The pathomechanism is inappropriate movement of the irrigating fluid through the zonules [1,2,10] when capsule is intact into the Berger's space or through the opening in the posterior capsule. This occurs usually towards the end of I/A where the residual cortex is irrigated. Four eyes had aqueous misdirection during or after cortical aspiration and 3 eyes after creation of ostium suggesting shallowing as a predisposing factor. Sudden intraoperative shallowing of the anterior chamber (surgical decompression) could be an initiating event. In one patient the IZHV opening was closed by a membrane and Nd YAG laser hyaloidotomy was performed. Anatomical success (deep anterior chamber) was achieved in all the eyes and there was no recurrence post operatively. In cases of combined surgery, IOP was under

control in all the eyes without the need for any medications in 2 eyes and the other 2 cases required medication.

To our knowledge, this is the first report on use of IZHV (anterior approach) as the management of acute intraoperative aqueous misdirection. We emphasize that choroidal hemorrhage must be excluded before IZHV is performed. Loss of red reflex and rapidly enlarging black brown mass must be actively looked for to rule out choroidal hemorrhage.[11,12] Our experience suggests IZHV can be an effective and safe solution for acute aqueous misdirection. Long-term mydriatic and cycloplegic therapy is mandatory.

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This paper was judged as the BEST PAPER of Glaucoma – II Session

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IN VIVO IMAGING OF THE SCHLEMM'S CANAL AND THE MANAGEMENT OF JOAG.

PURPOSE

To evaluate the presence of angle dysgenesis on ASOCT (ADoA) as a predictive factor for the management of Juvenile-onset open-angle glaucoma (JOAG)eyes.

METHODS

66 JOAG eyes with uncontrolled IOP were evaluated for the presence or absence of ADoA, which was defined as the absence of Schlemm's canal (SC) on ASOCT. B-scans in which SC was present were identified and quantified. Eyes that failed on medical management (MM) (including SLT) underwent trabeculectomy.

RESULTS

SC was identified as present in 100% (35) eyes that underwent successful MM vs 42% (13/31) eyes that showed failure and required surgery (**$p < 0.001$**). 93% (26/28) eyes in which SC was present in <50% ASOCT B-scans underwent surgery ($p < 0.001$). On regression analysis, the presence of SC increased the chances of success of MM by 2.9 times. **Conclusion:** The presence of ADoA (absence of SC on ASOCT) is a strong

predictor of failure of medical therapy in JOAG eyes and the need for trabeculectomy for IOP control.

INTRODUCTION

Juvenile open angle glaucoma (JOAG) eyes, like adult primary open-angle glaucoma (POAG), have an open angle; but these patients present with a higher baseline IOP and more severe glaucomatous visual field damage. In fact, at presentation, up to one-fifth of JOAG patients may be blind in one eye, and another 15% may have a bilaterally blinding disease.[1]

The increased IOP in JOAG is hypothesized to be due to abnormal aqueous outflow structures (angle dysgenesis), causing reduced aqueous drainage. Studies have demonstrated the presence of this isolated angle dysgenesis on gonioscopy (ADoG) and histopathology in JOAG eyes.[2–4] Owing to angle dysgenesis, IOP in half of JOAG patients tends to be refractory to maximal tolerated medical therapy and often requires surgical management.[5]

It has been previously demonstrated that JOAG eyes, while gonioscopically normal, may have an identifiable angle dysgenesis on ASOCT (ADoA). In a study on PCG, JOAG, POAG and healthy subject eyes, features of ADoA were identified as the absence of SC and presence of a hyperreflective membrane (HM)/abnormal tissue over trabecular meshwork. These features of ADoA were present in 100% of PCG eyes, 40% of JOAG eyes and none of the eyes of POAG and healthy subjects.[6] Infact, absence of schlemms's canal (presence of ADoA0 has been shown to be a predictor for outcomes of selective laser trabeculoplasty in JOAG eyes.[7]

METHODS

This prospective clinical cohort study from a tertiary eye center included consecutive JOAG patients who were willing to participate and gave a written informed consent. The study followed the tenets of the Declaration of

Helsinki and was approved by the institutional review board of the All India Institute of Medical Sciences, New Delhi.

JOAG patients included were those who met the following criteria: had been diagnosed between 10 - 40 years of age with IOP >22 mmHg in both eyes on two or more occasions, open-angle on gonioscopy in both eyes, with glaucomatous optic neuropathy in both eyes and corresponding visual field defects. The disease severity was staged using the Staging system of Mills et al.[8]

Patients excluded from the study were those with a history of steroid use, presence of any other retinal or neurologic pathology, evidence of secondary causes of raised IOP such as pigment dispersion, pseudoexfoliation, or trauma, those with any pathology detected on gonioscopy such as angle recession, irido-trabecular contact, peripheral anterior synechiae or ADoG like high iris insertion, iris processes or featureless angles.[9] Those eyes with poor visual acuity that precluded a proper fixation for examination were also excluded. We also had to exclude those eyes with poor quality images on ASOCT and patients who were lost to follow up.

A detailed history was taken, and an examination was performed for all individuals included in the study. All patients underwent goniophotography by an experienced glaucomatologist. Images were captured at optimum illumination and stored in the Eye Cap system (Haag Streit International, Koeniz, Switzerland), a digital photographic system attached to the slit lamp.

Evaluation of Angle dysgenesis on ASOCT: The OCT examination was performed using the Spectralis OCT (software version 6.5; Heidelberg Engineering GmbH, Heidelberg, Germany). All OCT scans were performed before initiation of treatment. The angle was imaged taking horizontal sections (at 3 and 9 o'clock). Instead of the angle module of the Spectralis,

we used the Sclera module to get dense scans of high resolution. Horizontal scans were taken without elevating the lid and thereby avoiding globe compression. The automated real-time (ART) scan was adjusted between 80 and 100 frames. The machine provided 25 scans for 15^{o} angle with a distance of 35µm between two scans. A total of 50 B-scans were obtained per eye (25 each at 3 and 9 o clock). Standardized and consistent indoor light conditions were maintained for each patient to prevent any alteration in the structure of angle by the pupillary dilation. In case of poor resolution, motion artifacts, excessive noise, or shadowing, the scans were repeated once. Using the device's inbuilt software, each EDI ASOCT B-scan image obtained was viewed at 400% magnification, centered around the irido-corneal angle for detailed viewing of the angle structures.

We looked for the presence of SC or a hyper-reflective membrane (HM) on ASOCT scans. Absence of SC and/or presence of HM were considered as features of Angle dysgenesis on ASOCT(ADoA) as have been previously described.[7] If SC/HM was identified in any one quadrant but absent in the other, it was considered as present for analysis.

Three glaucoma specialists (VG, SG, and KM) masked to details of the patients, evaluated the EDI ASOCT B-sans regarding the absence of SC and the presence of HM as indicative of ADoA. SC and HM were considered as present when atleast 2 (out of 3) observers agreed. One specialist (VG) also noted the total number of EDI ASOCT B-scans (out of 50 scans per eye) where the SC was visualized and determined whether SC was identified in ≥ 50% of EDI ASOCT B-scans (at least 26 out of 50 B-scans/eye) or not.

Treatment: All patients were initially provided with medical management (MM) which included topical glaucoma medications and/or selective laser trabeculoplasty (SLT). The SLT protocol has been previously described.[7] SLT

was offered to all patients as first line treatment, those patients who refused for SLT were given only topical glaucoma drugs. Success was defined as a reduction of IOP by 20% or more from the baseline IOP value at 6-months follow-up without any further IOP-lowering medication or surgery.

Those eyes which failed to attain adequate IOP control after MM underwent trabeculectomy. All patients were followed for upto 18 months.

STATISTICAL ANALYSIS

Baseline variables (clinical and demographic) of those showing SLT success were compared with those showing SLT failure. We used the independent 't'-test for continuous variables showing normal distribution, Mann-Whitney U test for continuous variables showing non-normal distribution, Fisher's exact test for categorical variables when more than 20% cells showed expected count less than 5 and Chi-square test for categorical variables when less than 20% cells showed expected count less than 5. The Shapiro Wilk test was used to analyze normality of the data. Average IOP reduction from pre-laser values was compared using the paired t-test. Correlation among variables was assessed by Spearman rank correlation for non-normally distributed continuous variables and Cramer's V for nominal variables.

Fischer's exact test was used to compare the outcomes of SLT with the presence or absence of ADoA. To determine agreement between two specialists on ASOCT features, Cohen's kappa test was used, and to assess agreement between all three specialists, we used Krippendorff's Alpha test.

A **Bias-Reduced Logistic Regression (maximum penalized likelihood)** analysis was carried out to assess the predictors associated with success of SLT. The variables found to significantly affect success (dependent variable) were entered in a logistic regression model. A p-value of <0.05 was considered significant. All analyses were performed using a statistical software package (SPSS for Windows, v. 26.0. SPSS, Inc, Chicago, IL).

RESULTS

Out of 70 eyes (one eye per patient) that met the inclusion criteria, 3 were excluded due to an inability to get good quality ASOCT images and 1 was lost to follow-up within a month. (**Figure 1**). The patients' demographic details and their baseline characteristics are presented in **Table 1.**

Evaluation of ASOCT: There was a good interobserver agreement between the three-glaucoma specialists in identifying SC or HM on ASOCT scans. There was a better interobserver agreement for the identification of SC (Krippendorff Alpha = 0.73) compared to the identification of HM (Krippendorff Alpha = 0.66). In 49 (74.2%) eyes, SC was identified as present by at least 2 observers, while in 40 (60.6%) eyes, all the three observers agreed on its presence. The SC could be identified in ≥50% per eye in 36 (54.5%) eyes. When all the three observers agreed, HM was identified as present in 11 (16.7%) eyes.

ADoA and management of JOAG: Overall, 35 eyes were successfully managed with medical management, while 31 eyes required a filtration surgery. Out of 49 eyes with presence of SC (as identified by atleast 2 observers), 35 (79.5%) eyes showed success of medical management. 97.2% (35/36) eyes with presence of SC on more than 50% B-scans showed success of medical management. All eyes (11/11) with presence of HM as agreed by all three observers, had a failure of medical management and required surgery. **Table 2** shows the comparison between baseline characteristics of eyes that underwent medical management vs. surgical management.

Variables that were significantly different between the cases with successful medical management vs those which required surgery were age of onset, vertical cup disc ratio, presence or absence of SC on ASOCT and presence of HM on ASOCT. These variables were entered in a Bias-Reduced Logistic Regression (maximum penalized likelihood) model. Using this model, we

observed that the presence of SC increased the chances of success of MM by 2.9 times. The absence of HM was not predictive in the model as its presence was invariably associated with the absence of SC.

DISCUSSION

As has been previously reported[7], this study reiterates that in JOAG eyes, without obvious features of angle dysgenesis on gonioscopy, there could be evidence of angle dysgenesis that can be appreciated on ASOCT. In-vivo analysis of the angle on ASOCT serves as a good predictor for determining outcomes of medical management in these patients.

In our study, when the baseline parameters were compared between the medical and surgical groups, it was observed that there was a statistically significant difference in age, pre-SLT vertical cup to disc ratio and number of pre-laser topical medications between the two groups. Failure of medical management among JOAG eyes was associated with younger age, greater vertical cup to disc ratio and greater pre-laser topical glaucoma medications. When tested in regression analysis, however, these factors were not significant predictors of failure of medical management.

With increasing life expectancy and relatively younger age of diagnosis, patients of JOAG will have to live with this disease for a longer time duration (as compared to POAG). This not only increases their risk of end-of-life visual disability, it also significantly lowers their health-related quality of life (QoL).[10–12] Further, they will have to bear a huge health related economic burden.[13] Previously it has been seen that, in a subset of JOAG patients (with no ADoG and ADoA), IOP can be controlled with SLT. This will greatly reduce their dependence on topical glaucoma therapy and the related economic burden.[13] Further they will have other advantages like lesser IOP fluctuations, no compliance related problems and no long-term ocular side effects as seen with glaucoma medications. We believe the ASOCT should be

included, in the management algorithm of these patients with JOAG. Keeping this in mind, we have proposed a simple treatment algorithm for JOAG eyes (**Figure 1**)

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Table 1: Demographic and clinical profile of JOAG patients

	N= 66
Age at time of diagnosis [range]	27.6 ± 8.8 [10-40]
Sex	
Male Female	50 (75.8 %) 16 (24.2%)
Ethnicity	Indian
Disease Stage	
Mild disease Moderate disease Severe/Advanced disease	27 (40.9%) 16 (24.2%) 23 (34.8%)
Best Corrected Visual acuity (LogMAR),	0.0 [0 to 1.5]
Refractive error No refractive error Low Myopia (<-3D) Moderate Myopia (-3 t0 -6D) High Myopia (>-6D)	 2 (3%) 30 (45.5%) 24 (33.3%) 12 (18.2%)
Baseline IOP (mm Hg)	33 ± 5
CCT (µm)	536.8 ± 32.4
Vertical Cup Disc Ratio	0.73 ± 0.17
Angle evaluation using Enhanced depth Imaging (EDI) on ASOCT	
Schlemm's Canal (when atleast 2 observers agreed) Present[a] Absent	 49 (74.2%) 17 (25.8%)
SC present in at least 50% B-scans (out of 50 scans/eye)	36 (54.5%)

Present Absent	30 (24.5%)
Hyperreflective Membrane (when all three observers agreed) Present Absent	 11 (16.7%) 55 (83.3%)
Outcome (on 18-months follow up)	
Treatment Medical Surgical	 35 (53%) 31 (47%)
Final IOP	

Data are N (%) or mean ± Standard Deviation (for normally distributed data) or median [range] (for non-normally distributed data). SLT=selective laser trabeculoplasty. JOAG=Juvenile primary open angle glaucoma. CCT=central corneal thickness. IOP= Intra-Ocular pressure. SC – Schlemm's Canal

[a]Schlemm's Canal was considered as present when observed on at least two consecutive B - scans (to differentiate it from artifacts).

Table 2: Comparison between baseline characteristics of eyes that underwent medical management vs. surgical management.

	Medical management	Surgical management	p-value
Number	35	31	
Age (years)	29.3 ± 9.7	25.5 ±7.6	0.06#
Sex • Male • Female	 28 (80%) 7 (20%)	 23 (61,3%) 8 (88.6%)	0.9§
Disease stage • Mild disease • Moderate disease • Advanced/Severe disease	 22 (62.9%) 7 (20%) 6 (17.1%)	 5 (16.2%) 9 (29%) 17 (54.8%)	0.001§
BCVA (LogMAR)	0.0 [0 to 0.78]	0.0[0 to 1.5]	0.84*
Refractive error • No refractive error • Low Myopia (<-3D) • Moderate Myopia (-3 to -6D) • High Myopia (>-6D	 2 (5.7%) 14 (40%) 13 (37.1%) 6 (17.1%)	 0 16 (51.6%) 9 (29%) 6 (19.4%)	0.08§
Baseline IOP (mm Hg)	31.06 ± 4.3	35.45 ± 4.8	<0.001#
CCT (µm)	540.44 ±29.4	532.07 ±38.6	0.31#
Vertical Cup Disc Ratio	0.67 ± 0.16	0.81 ± 0.13	<0.001#
Angle evaluation using Enhanced depth Imaging (EDI) on ASOCT			
Schlemm's Canal (when all 3 observers agreed) Present*	35 (100%)	14 (45.2%)	<0.001§ (Cramer's V= 0.62)

Absent	0	17 (54.8%)	
SC present in at least 50% B-scans (out of 50 scans/eye) Present Absent	33 (94.3%) 2 (5.7%)	3 (9.7%) 28 (90.3%)	<0.001^ (Cramer's V= 0.84)
No. of B-scans in which SC was identified (out of 50 scans/eye)	41 [6 to 50]	0 [0 to 40]	*<0.001
Hyperreflective Membrane (when all three observers agreed) Present Absent	0 (0%) 35 (100%)	11 (35.5%) 20 (64.5%)	<0.001§ (Cramer's V= 0.47)

[a] Schlemm's Canal was considered as present when observed on at least two consecutive B - scans (to differentiate it from artifacts).

Data are N (%) or mean ±SD (for normally distributed data) or mean [range] (for non- normally distributed data).

BCVA= Best corrected visual acuity, HM – Hyper-reflective membrane, IOP= Intra-Ocular pressure, JOAG=Juvenile primary open angle glaucoma, SC – Schlemm's Canal

Statistical tests: # Independent t-test, § Fischer's exact test, * Mann Whitney U test, ^ Chi squaretest

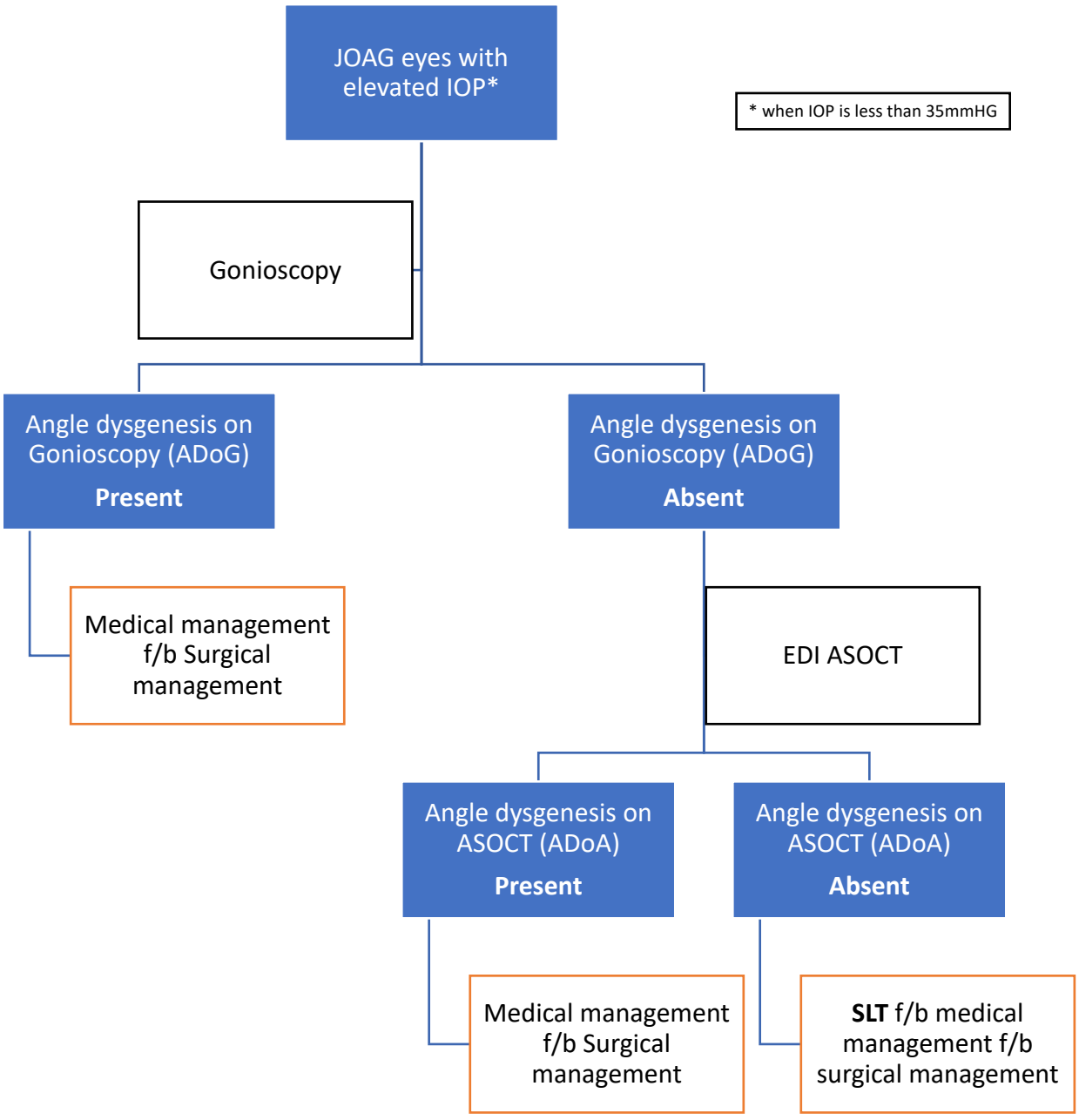

Figure 1 – Proposed management algorithm for JOAG.

This paper was judged as the BEST PAPER of Glaucoma - III Session

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FRUGAL SMARTPHONE BASED GONIO-IMAGING DEVICE: A VALIDATION STUDY

ABSTRACT

Purpose: This study aimed to validate the anterior chamber grading done on the images obtained with DIGS by comparing with the gold standard gonioscopy by slit-lamp biomicroscopy.

Design: A prospective observational study was designed for the validation.

Participants: 222 images were required to validate the technique at 90% power and alpha of 0.05 for Cohen's kappa agreement. With the gradable image acquisition rate of 80% in the pilot study, 278 images were required to meet the minimum sample size. Out 280 images obtained, 250 were found to be of gradable quality.

Methods: Gonioscopy on slit-lamp biomicroscope was performed by a single masked physician. Gonioimaging using DIGS was performed by another masked physician. The gradable quality images were then graded in masked fashion by two physicians and compared to the gold standard slit-lamp gonioscopy.

Main Outcome Measures: The primary outcome was to classify the anterior chamber angles into two broader categories – open angle and closed angle by use of smartphone gonioimaging.

Results: The intra-observer agreement (between slit-lamp gonio-evaluation and gonio-imaging grading by DIGS) was 84.0% with Cohen's kappa 0.65 which signified substantial agreement. The interobserver agreement between two physicians for the grading of gonio-imaging using DIGS was 92.4% with Cohen's Kappa 0.71 which signified substantial agreement.

Conclusions: DIGS is a new, frugal innovation that can be helpful in screening the patients for their anterior chamber angle status by obtaining high gradable quality images.

Glaucoma is the second most common cause of blindness in the world and the leading cause of irreversible blindness. An estimated 12 million people suffer from the disease worldwide. It is the second leading cause of blindness in the adult population in India. With the disease-causing irreversible blindness, it has been realised as a major health burden for the country. It has been divided into two broad categories of open-angle and closed-angle glaucoma based on the gonioscopy findings. Primary open-angle glaucoma (POAG) is estimated to be more common than primary closed-angle glaucoma (PACG), but Asian population has almost equal distribution of patients among these two categories. Vellore eye study (VES), a population-based survey in India has estimated a staggering 10.3% of the population having occludable angles or angle-closure glaucoma. (1) Other population-based surveys in India also have similar findings. (2–4) The only method to diagnose angle status of persons with occludable angles (OA), primary angle closure suspects (PACS) or PACG is by performing a gonioscopy. Baseline gonioscopy is also indicated in all cases of glaucoma and glaucoma suspect to classify and decide on the management.

Unfortunately, the gonioscopy is not performed on initial evaluation in 48.7% of the patients as reported by Hertzog. (5) A survey on the performance and training of gonioscopy by Feng et al shows that one-fifth of

the participants were not confident in the skill, while a quarter of respondents were dissatisfied with the quality of training received. (6) Astonishingly 81% of the respondents from the junior residency were not confident in gonioscopy, who primarily are the first point of contact with the patients, either in hospitals or in public outreach screening camps. (6)

In rural India, the first point of contact for >50000 patients are primary level physicians or technicians in a resource-strapped primary vision centre. (7) Affordable, portable and user-friendly equipment and innovations can allow these centres to be converted into tele-screening points where the patients can be screened and can be called to the higher centres if required. Smartphone imaging has caught the imagination of innovators for being an affordable and highly mobile option with in-built telecommunication capabilities. With the advancement in camera capabilities of smartphones, high-quality images are now possible to be acquired without a bulky and costly instrument. Ophthalmology has been the forefront of smartphone imaging applications in medical field. Numerous smartphone-based fundus imaging devices have been innovated and successfully used to date. The authors have innovated and implemented a low-cost fundus imaging device MII-RetCam in Smart-ROP programme, a telecommunication based ROP screening model. (8)

Unfortunately, similar innovations have not taken place in anterior segment ophthalmic imaging. Most of the anterior segment imaging modules are dependent on slit-lamp adapters and thus lose on the portability. Gonio-imaging has been previously attempted with RetCam-120 but has not got a wider public acceptance. (9) The lack of portability and cost involved in procuring the machine may be the reason behind it.

With the magnitude of social burden glaucoma is proving to be, a need for a low-resource requiring screening tool which can be utilised in outreach

camps as well as in eye hospitals is felt. The authors have described a smartphone-based gonio-imaging technique which utilises a 4-mirror goniolens and the stock camera app of the smartphone to image the anterior chamber angle. (10) Direct imaging of goniomirror by smartphone (DIGS) does not require any other instruments such as adapters or slit-lamp and thus utilises minimum resources and can be implemented in any settings. This study aimed to validate the anterior chamber grading done on the images obtained with DIGS by comparing with the gold standard gonioscopy by slit-lamp biomicroscopy.

MATERIALS AND METHODS

A prospective observational study was designed to validate the outcomes of direct imaging of goniomirror by smartphone (DIGS). The sample size was calculated to be 222 images at 90% power and alpha of 0.05 for Cohen's kappa agreement. (11) With the gradable image acquisition rate of 80% with the pilot study, 278 images were required to meet the minimum sample size. Imaging with 4-mirror goniolens yielded 4 photographs of 4 different quadrants and so 70 eyes were aimed to be imaged sequentially to fulfil the sample size.

The Institution's Ethics committee clearance was obtained and the study adhered to the declaration of Helsinki. The patients visiting the glaucoma clinic of a tertiary care hospital were considered as the cohort under observation, with the assumption of the patients presenting with varying gonioscopic findings which can be imaged and compared. The informed consent was taken from every patient before the imaging. Each patient was then evaluated for their visual acuity, anterior segment examination, gonioscopic evaluation and undilated evaluation of central fundus and IOP recorded with Goldmann's applanation tonometer. The gonioscopic evaluation on slit-lamp biomicroscope was done by a single physician (RS)

for all the eyes using a 4-mirror flanged indirect goniolens (Volk Optical Inc., USA). Eyes with grade 3 or above on Spaeth grading of gonioscopy were placed in an open-angle group, and grade 2 or below were placed in a closed-angle group. The anterior chamber angle of the patients was then imaged by using the same goniolens and OnePlus 6 smartphone's (OnePlus, China) using the DIGS imaging technique by a masked physician (NK). The technique involved placing the 4-mirror flanged goniolens on the cornea with patient in sitting position. (Figure 1) The stock camera app of the smartphone was used for imaging. The centre of the camera lens was aligned with the pupil by using the grid lines of the camera app. The centration helped to ensure that all 4 mirrors are imaged simultaneously. The images were obtained with flashbulb of the camera acting as light source. 3 images of each eye were taken. The best image for each quadrant from each eye was then chosen and extracted. The images were then transferred to AS for codification of the filenames and storage. The masked images without any identifiable data were then reviewed again by RS on a later date in batches of 50 photographs to evaluate the agreement between the gold standard slit lamp gonioscopic finding with the new imaging technique. The images were also reviewed by another expert KS for evaluating the inter-observer agreement of the findings.

The quality of the image was classified into gradable and non-gradable based on the following criterion adapted from the study by Azad et al. (9)

Grade 1: All angle landmarks clear and well-focused in all quadrants

Grade 2: Some angle structures clear, others blurred in some quadrant

Grade 3: Angle landmarks could not be ascertained in any quadrant due to blurring or view hampered by reflections.

Grade 1 and Grade 2 images were considered as gradable images were Grade 3 image was considered as non-gradable. As the image of each quadrant was

separately stored and evaluated, blurred quadrants of images in Grade 2 photographs were not assessed.

The primary outcome was to classify the anterior chamber angles into two broader categories – open angle and closed angle by use of smartphone gonioimaging, and to co-relate the findings with the gold-standard slit lamp evaluation. The secondary outcomes were to evaluate the efficacy of the technique in imaging any other gonioscopic findings such as pigmentation of trabecular meshwork, peripheral anterior synechiae, angle recession, neovascularisation, presence of blood or foreign body etc.

The grading from both evaluators was entered into an excel sheet and stored. The agreement was calculated using Cohen's kappa coefficient formula in IBM SPSS v20 (IBM).

RESULTS:

70 eyes were sequentially imaged to obtain images of 280 quadrants for the validation study. Out of obtained 280 images, 250 images were of gradable quality. These images were graded by both the observers in 5 batches of 50 photographs. 39 out of 70 eyes (55.7%) were classified with an open angle on slit-lamp gonioscopy and rest 31 eyes (44.3%) were classified with closed angle.

The intra-observer agreement (between slit-lamp gonio-evaluation and gonio-imaging grading by DIGS) for RS was Cohen's kappa 0.6549 (SD 0.075, 95% CI 0.5078-0.802) which signifies substantial agreement. The interobserver agreement between RS and KS for the grading of gonio-imaging using DIGS was Cohen's Kappa 0.82 (SD 0.0557, 95% CI 0.7189-0.9371) which signified substantial agreement. 91.6% agreement was found between the level of pigmentation noted on slit-lamp evaluation and gonio-images obtained from DIGS.

Other additional findings noted on slit-lamp gonioscopy are tabulated in table1, and such findings reported on the DIGS by both reviewers are expressed in percentage alongside. No new findings were reported on DIGS that was not reported on slit-lamp gonioscopy.

DISCUSSION:

Gonioscopy is an essential component of glaucoma diagnosis and determines the line of management. Patients having OA, PACS or PACG require immediate LASER peripheral iridotomy (PI), and the conditions can only be assessed using gonioscopy. The current study provides a cost-effective frugal innovative technique to screen for open or closed-angle of the anterior chamber. It provides a clear gradable image in 80% of the photographs obtained with sufficient details.

The lacunae in gonio-screening have been attributed to the skill itself not being acquired, the dependence on slit lamp to perform the examination and the time it requires. The described technique allows for a faster, slit lamp free gonio-screening. This translates it for having the potential to be utilized in glaucoma screening in outreach camps where the basic slit-lamp evaluation is often not deployed.

Our study reveals a prevalence rate of the open angle at 55.7% and the rest have some form of angle closure. The study population was Indian population, where the rate of prevalence of open and closed-angle glaucoma is postulated to be equal. (12) The study though is not designed for deriving prevalence rate, agrees to the distribution. The study was conducted in the glaucoma clinic of a referral tertiary centre which might have an impact on disease distribution. The glaucoma diagnosis has not been established in this study as the visual field evaluation and disc evaluation was not taken into the account.

The authors do realise that this technique is not without limitations. The image sensor of the smartphone is small in size and thus high-resolution images cannot be obtained. Pinch and zooming of the obtained images cannot give sufficient details to identify subtle pathologies like angle neovascularization. The technique is flashlight dependent and thus dim-light gonioimaging cannot be performed with DIGS. Authors are in the process of developing a device that has potential to overcome most of the limitations.

DIGS is a new, frugal innovation that can be helpful in screening the patients for their anterior chamber angle status. Good quality images can be obtained to segregate the patient that might need intervention for a closed or opposable angle. These patients can further be counselled and treated, thus lowering the disease burden.

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Table 1: Gonioscopic findings noted on slit-lamp gonioscopy and agreement of two observers (expressed in percentage)

Findings	On slit-lamp gonioscopy	Observer 1 (RS)	Observer 2 (KS)
Peripheral anterior synachiae	4	4 (100%)	4 (100%)
Iridodialysis cleft	2	2 (100%)	2 (100%)
Angle recession	3	3 (100%)	3 (100%)
Blood in Schlemm's canal	2	1 (50%)	1 (50%)
Blood in anterior chamber	2	2 (100%)	2 (100%)
Neovascularisation of angle	3	0 (0%)	0 (0%)
Silicone oil in anterior chamber	2	2 (100%)	2 (100%)

This paper was judged as the BEST PAPER of Lacrimal Session

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A STUDY ON PROBLEMS FACED BY RESIDENTS IN LEARNING AND PERFORMING EXTERNAL DACRYOCYSTORHINOSTOMY

METHODS:

A questionnaire was prepared and circulated among all residents of a tertiary care centre. Residents were expected to have performed at least fifteen dacryocystorhinostomy surgery in order to participate in this study. Responses were recorded and subjected to statistical analysis.

RESULTS: A total of 35 responses were obtained from junior and senior residents. Residents from first year experienced difficulty majorly in planning incision, angular vein management, suturing and nasal packing. Second year residents found problem in cutting of posterior flaps, bone cutting and nasal mucosa protection. Third year residents and senior residents in conjunction faced major issue in dealing with cosmesis, fistula handling, NLD tube implantation and positioning and tenting of flaps.

CONCLUSION: External dacryocystorhinostomy is gold standard treatment for chronic dacryocystitis and efforts should be taken to train residents efficiently according to problems faced by residents.

Keywords: Dacryocysorhinostomy, Chronic dacryocystitis

INTRODUCTION:

Chronic dacryocystitis is a prominent cause of ocular morbidity in our country amounting to almost majority of epiphora causes. Watering of eyes may be the result of excessive tear production, abnormalities of lid position or movement, lacrimal canalicular pump failure, or obstruction of the outflow tract. Nasolacrimal duct obstruction either primary or secondary is one of the important causes of epiphora, the most common cause being chronic dacryocystitis.[1]

External dacryocystorhinostomy (DCR) was first described by Toti in 1904.[2] With external DCR, the lacrimal sac is directly incorporated into the lateral wall of the nose, so that the canaliculi drain directly into the nasal cavity.[3]External DCR remains the gold standard surgical treatment modality for epiphora due to lacrimal passage obstruction beyond common canaliculus for more than 100 years.[4]Ohm (1920) was the first to advocate anastomosis of nasal mucosa to sac.[1].In 1921, Dupuy-Dutemps and Bourget supported mucosal anastomosis with suturing of mucosal flaps over periosteum.[5] Success rate of external DCRvaries from 82% to 99%.[6]

Failure of external DCR occurs mainly due to obstruction of common canaliculus, postoperative soft tissue infection and closure of osteotomy site by granulation tissue.[11] Success rate of surgery can be increased by making a large ostium, adequate exposure of lacrimal sac, good anastomosis of flaps, reducing postoperative infections and making an epithelized tract between sac and middle meatus.[12] Hence we decided to find out problems faced during residency curriculum while learning and performing external dacryocystorhinostomy.

MATERIAL AND METHODS:

This cross-sectional observational study was conducted in tertiary eye care center, from October 2021 to September 2022. The study was approved by

Institutional Ethical Committee and Tenets of Declaration of Helsinki was followed.

All patients attending Ophthalmology outpatient department and presented with symptoms of epiphora with or without discharge or swelling at sac area were included in this study. Probing and syringing were done in all cases and diagnosed with primary acquired nasolacrimal duct obstruction and chronic dacryocystitis with or without mucocele.

All patients with primary acquired nasolacrimal duct obstruction (PANDO) and above 20 years of age were operated by junior residents of all the three years under supervision of senior consultants. Patients who suffered from acute dacryocystitis, secondary acquired nasolacrimal duct obstruction (SANDO), failed DCR, canalicular and punctal occlusion, lower eyelid deformity (entropion, ectropion or lid laxity), nasal mucosa pathology (atrophic rhinitis, lupus etc.), bleeding diathesis and suspected lacrimal sac malignancy were excluded from the study.

A questionnaire was prepared and circulated among all residents of a tertiary care centre. Residents were expected to have performed at least fifteen dacryocystorhinostomy surgery in order to participate in this study. Responses were recorded and subjected to statistical analysis. All cases underwent detailed history and thorough examination of each eye, including examination of lacrimal drainage system for swelling, tenderness, fistula, regurgitation test. Lacrimal syringing was done in all cases along with primary and secondary Jones dye test. Anterior rhinoscopy was done to rule out gross nasal pathologies and physician checkup for surgical fitness was obtained in all patients. Pre-operative investigations included complete hemogram, blood sugar, bleeding time, clotting time and prothrombin time. Dacryocystography was done in all cases. Written and informed consent was obtained from patients / relatives.

Surgical Protocol

Surgery was performed by single surgeon along with two assisting surgeons. Intraoperative and postoperative observations were recorded and analysed by different a person. 4% xylocaine was instilled in ipsilateral nasal cavity to anaesthetize nasal mucosa. Nasal cavity was packed with xylocaine-soaked pack.A curvilinear incision of 10 mm length corresponding to anterior lacrimal crestwas deepened through orbicularis muscle and muscle was separated by blunt dissection to expose anterior lacrimal crest. Cat's paw retractors were inserted into either side of incision and lacrimal fascia was incised 1 mm lateral to anterior lacrimal crest dividing bony attachment of the medial canthal ligament with a blunt dissector. Thereafter, periosteum was dissected from lacrimal fossa by inserting periosteal elevator. Bony ostium was created by removing anterior lacrimal crest down to entrance of nasolacrimal duct. The bony opening was enlarged with Citelli's bone punch up to 10 x 12 mm in diameter taking care to preserve nasal mucosal membrane intact.The margins of osteotomy were smoothened.

An 'H' shaped incision was made through medial wall of the sac so as to form anterior and posterior flaps of lacrimal sac. The nasal mucosa was incised in a similar fashion along the upper and lower limit of oval opening for its full diameter. Thereafter, anterior and posterior mucosal flaps of lacrimal sac and nasal mucosa were sutured with two to three 6-0 vicryl interrupted sutures. The surgical wound was closed in layers. Orbicularis muscle was closed with 6-0 vicrylsutures and the skin incision by interrupted or continuous subcutaneous sutures using 6-0 black braided silk sutures and a firm pressure dressing was done after antibiotic ointment application. Nasal packing was removed.

Postoperatively, all patients were given systemic and topical antibiotic drops and nasal decongestant drops four times a day for one week. First dressing

and lacrimal irrigation was done after 24 hours. Skin sutures were removed after 10 days.

Follow-up examination was scheduled on the first and tenth postoperative day and thereafter at 1, 3 and 6 months. At each follow-up visit cases were examined and enquired for any complications. The surgical success was defined by the anatomical patency of lacrimal drainage system on irrigation at final follow-up. Blocked syringing was considered as surgical failure. Cases with non-patent lacrimal irrigation underwent nasal endoscopy and Dacryocystography to know the level of obstruction.

STATISTICAL ANALYSIS

Data were analysed using SPSS 16.0 software. P value < 0.05 was considered significant.

RESULTS:

A total of 35 responses were obtained from junior and senior residents. All residents belonged to age group of 25-34 years. Among residents 11 were males and rest females. Thirty of them were junior residents with ten each in first year, second year and third year of their residency curriculum and remaining five of them were senior residents. As a part of our study, responses from third year residents and senior residents were taken as one group.

Table 1: Table showing number of surgeries performed by residents

Surgeries performed in number	number
First year resident	15-20
Second year resident	30-70
Third year resident	80-120

Table 2: Table showing difficulties faced by different residents while performing external dacryocystorhinostomy

Problems faced	First year resident (10)	Second year resident (10)	Third year and senior resident (15)
Incision making	2	-	-
Angular vein	8	-	-
Nasal packing	3	-	-
Suturing	1	-	-
Bone cutting	8	4	-
Nasal mucosa	9	3	-
Cutting of flaps	10	5	1
Cosmesis	10	9	4
Fistula	10	10	6
NLD tube	10	10	4
Positioning of flaps	10	8	7

Residents from first year experienced difficulty majorly in planning incision, angular vein management, suturing and nasal packing. Second year residents found problem in cutting of posterior flaps, bone cutting and nasal mucosa protection. Third year residents and senior residents in conjunction faced major issue in dealing with cosmesis, fistula handling, NLD tube implantation and positioning and tenting of flaps.

Anatomical success rate was above 90 percent in surgeries performed by third year residents while it was 75-80 percent in first and second year residents. The success rate gradually increased during training program as the junior residents increased their number of cases.

DISCUSSION

We found low failure rate of around 6 percent in third year students who had performed a minimum of 80 surgeries during their third year residency program. Both the anatomical and functional success rate was higher as there were no failures in last 20 cases performed by them. Similarly the complications also reduced significantly.

Kashkouli et al did a retrospective analysis of 276 cases of external dacryocystorhinostomy by trainees but didnot provide information on learning curve.[] Mirza et al in 2002 reported an improved outcome in 38 out of 76 cases of endonasal dacryocystorhinostomy but didnot provide information about learning curve.[]

CONCLUSION:

External dacryocystorhinostomy is gold standard treatment for chronic dacryocystitis and efforts should be taken to train residents efficiently according to problems faced by residents.

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MACULAR MICROVASCULAR AND STRUCTURAL CHANGES IN NEUROMYELITIS OPTICA SPECTRUM DISORDERS (NMOSD) AND MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY (MOGAD)

INTRODUCTION

Neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein antibody disorder (MOGAD) are both autoimmune demyelinating disorders of the central nervous system[1]. The retina and optic nerve being a part of the central nervous system are affected in these disorders leading to ocular manifestations in these diseases, typically optic neuritis which can lead to visual impairment or even blindness[2]

There is a significant overlap between the clinical presentation of NMOSD and MOGAD in the acute clinical setting, however it is essential to establish an accurate diagnosis as this may affect treatment strategies and outcomes. Confirmatory lab tests like testing for aquaporin-4 antibody (AQP4) or myelin oligodendrocyte glycoprotein (MOG) antibody might be unavailable, expensive and time consuming. [3,4]

Besides the well-established immune mediated mechanisms that play a role in autoimmune neuroinflammatory, vascular and metabolic factors are being recognised to play an important role as well[4]. Optical coherence tomography angiography (OCTA) is a new non-invasive and rapid investigative modality

that has already been used to observe changes in the retinal nerve fibre layer, ganglion cell inner plexiform complex and retinal microvascular density in aquaporin-4 antibody seropositive neuromyelitis optica spectrum disorders.[5]

In this observational cross-sectional study, we have used OCTA to delineate aforementioned structural and microvascular changes in NMOSD and MOGAD to better understand the pathophysiological changes in these disorders and aid in their rapid diagnosis and apt management. Methods

This was an observational cross-sectional study in which 17 MOGAD, 8 NMOSD and 10 controls were enrolled, the study was carried out in the neuro-ophthalmology department of a tertiary eye care centre in southern India, and data was collected over a period of 6 months.

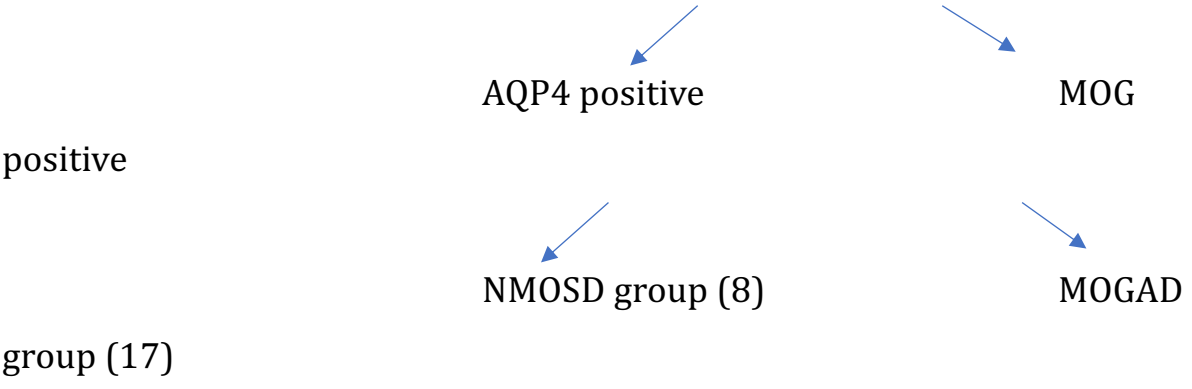
Patients presenting to the neuro-ophthalmology OPD with clinical features suggestive of autoimmune neuroinflammatory disorders were subjected to OCTA imaging for both eyes and aquaporin-4 as well as MOG antibody testing after taking an informed consent for participation in the study.

The diagnosis and grouping of patients was based on serology, AQP4 positivity confirming the diagnosis of NMOSD and MOG antibody positivity confirming the diagnosis of MOGAD respectively. For comparison 12 healthy age and gender matched controls were enrolled in the study who underwent OCTA imaging only, for both eyes.

The key parameters measured and compared were ganglion cell and inner plexiform layer thickness (micrometres) and macular vessel density (mm/mm^2)

OCTA specifications – spectral domain OCTA (SD OCTA) using Zeiss Cirrus™ 6000 Angioplex™

1. Clinical suspicion of NMO or MOGAD → OCTA + AQP4 and MOG antibody testing



2. Healthy controls – age and gender matched (10) → OCTA

3. Parameters measured for statistical analysis – GCIPL thickness (micrometres) and macular vascular density (mm/mm^2)

4. Unpaired t-test carried out for all groups and affected as well as unaffected eyes within each group and results analysed.

RESULTS

The following were the characteristics of the study population.

Table 1 Showing the distribution of characteristics amongst study population.

Parameter		NMOSD group	MOGAD group	Control group
Average Age (years)		39.6	36.9	36.9
Sex	male	1 (12.5%)	6 (35%)	3 (30%)
	female	7 (87.5%)	11 (65%)	7 (70%)
Laterality	unilateral	8 (100%)	9 (53%)	NA
	bilateral	0 (0%)	8 (47%)	

Average interval between onset of symptoms and investigation (months)	3.0	2.9	NA
Average visual acuity of affected eye at presentation (LogMAR)	2.42	1.13	NA
Average final visual acuity of affected eye (LogMAR)	0.77	0.15	NA

The following were the results of the data collection.

Table 2 Averages of collected data.

Variable measured	NMO group		MOGAD group		Control group
	Affected eye	Unaffected eye	Affected eye	Unaffected eye	Healthy eye
Average macular vascular density (ETDRS perfusion density %)	16.6	18.0	16.0	18.6	31.8
Average ganglion cell + inner plexiform layer thickness (micrometers)	52.4	68.5	53.1	66.5	69.67

Upon carrying out multiple student t-tests the following were the p values obtained.

Table 3 Comparison of NMO group with controls. (* indicates statistically significant results considering p<0.05)

Variable compared	p Values		
	NMO affected eyes compared to controls	NMO unaffected eyes compared to controls	NMO affected eyes compared to NMO unaffected eyes
Macular vascular density	0.0002*	0.0048*	0.1228
Average ganglion cell + inner plexiform layer thickness	0.0016*	0.5398	0.0091*

Table 4 Comparison of MOGAD group with controls. (* indicates statistically significant results considering p<0.05)

Variable measured	p Values		
	MOGAD affected eyes compared to controls	MOGAD unaffected eyes compared to controls	MOGAD affected eyes compared to MOGAD unaffected eyes
Macular Vascular density	0.0001*	0.0012*	0.3207
Average ganglion cell + inner plexiform layer thickness	0.0003*	0.0009*	0.1472

Table 5 Comparison of NMO group with MOGAD group. (* indicates statistically significant results considering p<0.05)

Variable measured	p Values	
	NMO affected eyes compared to MOGAD affected eyes	NMO unaffected eyes compared to MOGAD unaffected eyes
Macular vascular density	0.7814	0.6321
Average ganglion cell + inner plexiform layer thickness	0.8876	0.5622

CONCLUSION

NMO showed a strong female predisposition and had a unilateral presentation in contrast to MOGAD which had an equal distribution in terms of sex, while being bilateral in most cases. Visual deficit was more severe in NMO compared to MOGAD, NMO also had a poorer visual recovery compared to MOGAD.

Macular vascular density (MVD)

There was a significant reduction in MVD in NMO and MOGAD affected eyes compared to healthy controls. What is interesting however, is that even NMO and MOGAD unaffected eyes showed significant reduction in MVD compared to healthy controls. NMO and MOGAD affected eyes did not show a significant difference between macular vascular density compared to NMO and MOGAD unaffected eyes.

Ganglion cell + inner plexiform layer (GCIPL) thickness

NMO and MOGAD affected eyes had a statistically significant thinning of GCIPL compared to healthy controls. NMO unaffected eyes did not have significant thinning compared to controls, however MOGAD unaffected eyes did show significant thinning compared to controls. NMO affected eyes had significant thinning of GCIPL compared to their unaffected counterparts, however MOGAD affected and unaffected eyes did show a statistically significant difference in GCIPL thickness

DISCUSSION

The findings of this study resonated well with the pre-existing evidence about NMO and MOGAD in terms of gender wise distribution, laterality and effect on visual acuity [6,7].

The fact that decreased macular vascular density was universally present in patients of both these diseases irrespective of whether the eye was affected or not gives an insight into the systemic nature of these diseases and demands need for further research into the vascular and metabolic features

of these disorders. It has already been demonstrated that hyalinisation of small vessels and perivascular inflammatory infiltrates are one of the earliest pathological changes in NMO[8]. AQP4 antibodies in NMO target AQP4 channels which are abundant in perivascular astrocytic foot processes justifying the changes in vasculature as well[9]. Vascular changes in MOGAD still need to be studied in greater detail and no pathophysiologic evidence is present regarding the same currently.

As far as subclinical disease is concerned, this study has not found any subclinical OCT/OCTA changes that fulminated into a subsequent symptomatic illness in either NMO or MOGAD patients, however a longer follow up is required to be able to comment about the same.

Microvascular changes were universal in NMO as well as MOGAD be it affected or unaffected eyes, however GCIPL thinning in the healthy eye was noticed more with MOGAD and could be an insight into the more common bilateral presentation of the disease, the molecular mechanisms of the same need to be better understood.

When we compare our findings to the recently published study by Lang et al. the findings of reduction in MVD in both affected and unaffected eyes are common to both studies. However they found a significant difference in GCIPL thinning between affected and unaffected eyes in both NMO and MOGAD, in contrast to our study where this difference was seen only in the MOGAD group.

It is still to be determined if OCTA can pick up pre-clinical changes in NMO and MOGAD and longer and closer follow ups will be required to determine the same in future, but looking at the theoretical pathophysiology of the disease and the changes seen after the disease has set in, we believe that this investigative modality can prove to be of great significance in the early diagnosis and management of these disorders.

In terms of limitations of the study, there was a mismatch of the number of samples in the NMO and MOGAD study groups and more patients need to be evaluated for changes in MVD and GCIPL thickness. A better control of the duration after which the investigations are being performed on the patients, after the onset of symptoms, can give a better frame of reference to the changes observed. In our study the average duration of symptoms after which the scans were done was around 3 months, with a high variability however, owing to poor follow up of these patients in our setting. In our study, only the superficial vascular plexus was studied, as it is closest to where the pathophysiology of these disorders is occurring, however a multivariate analysis of superficial, intermediate and deep capillary plexus could lead to a more holistic insight into the vascular changes occurring in NMO and MOGAD.

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This paper was judged as the BEST PAPER of Neuro Ophthalmology – II Session

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EYE MG MAX/A COMPREHENSIVE NEURO-OPHTHALMOLOGY 3D TOUCH INTERFACE APPLICATION WITH AUGMENTED REALITY

ABSTRACT:

To make neuro-ophthalmic concept learning and e-counselling better, we have innovated a 3D with augmented reality (AR) application (Eye_MG_Max) built on an advanced interactive 3D touch interface. Concepts of neuro-ophthalmology (circle of Willis, cavernous sinus, cranial nerves, visual pathway etc.) have lots of theoretical frameworks. Neophyte residents and patients may have to mentally visualize them during training and counseling respectively. Only a powerful cognitive tool like a 3D atlas, where users can choose their optimal frame, cross-section, and amount of zoom required to visualise various parts of the neuroanatomy structures, can fill in their cognitive mental gaps. Majority of users have already been using their smartphones to surf the internet for studying as well as to understand the disease process. e-Ophthalmology is the order of the day; thus, carving a mobile application with user-friendly 3D augmented reality pertaining to anatomy and pathophysiology of neuro-ophthalmology is the way forward.

KEYWORDS:

Eye MG Max, 3D, Augmented Reality, Neuro-Ophthalmology

FULL TEXT :

In this era, medical education is gradually flourishing with advancements of the technologies. Various innovative and interactive smart mobile applications pertaining to neuro ophthalmology, playing essential role in learning resources, counselling, and surgical simulations, for ophthalmologists. Nowadays, augmented reality (AR) technology is not a science-fiction concept, stepped foot into the science-based reality. Currently, reality-based applications are more helpful to know human anatomy via three dimensions. The use of an e-ophthalmology platform with AR will pave the pathway for new-age gameful pedagogy, better comprehensive counselling. In this paper, we have reported on one such novel innovative augmented reality application along with touch-interference facilities named as “Eye MG Max” to aid in pedagogy and counselling.

THE INITIATION OF “EYE MG MAX” TOUCH-INTERFERENCE APPLICATION

Modern technologies are more widely used in the healthcare industry for easy diagnosis of the disease and e-counselling process. In this digitalization era, medical professionals and neophytes showing interests in using reality-based technology in their studies or practice. Recently, Ramesh et al. introduced AR technology in android platform for simplifying concept learning about complex anatomical and pathological structures of the eyeball. In android platform, the primary drawback of the AR application is the AR template, which is needed to be printed and kept on table or surface

before operating the application. Moreover, the touch-interference facility is not available.[1-5]

"Eye MG Max" application is fully concentrated to give a cutting-edge technology experience with augmented reality and touch-interference in neuro ophthalmology and established gamified fun learning. There are multiple 3D models integrated into a single prototype view. Ophthalmologists and novices can view these 3D models in a very realistic way to learn about the complex anatomical and pathological structures of organs(brain, visual pathway, circle of Willis, venous system). It is more convenient for users to see the different angles of the model's structure through free rotation, dragging and zooming views, etc. Moreover, this application briefly explains about the models in the real world using an AR camera.

FEATURES OF THE NOVEL APPLICATION

3D view: For illustration purposes, anyone can view the whole 3D model in 360-degree angles using the "Hide and Show button". There are some customized angles available to split the model into different associated parts of the 3D models. These models help to know the eye structure along with brain and its functionality with the animated actions. The transparency mode is available for observing the internal organ structures such as brainstem, cerebral venous system, nucleus and visual pathway etc.

AR View: AR view is one of the advanced modules in this application. This section has an augmented reality camera mode (RGB Camera) and Light detection and ranging sensor(LiDAR). The LiDAR sensor senses the area around us and maps the real world to the virtual world. On switching the AR view, the AR camera asks for permission to activate the AR session. Once the AR session starts, there are some options given, to choose the 3D model. After choosing and establishing the 3D models in the appropriate location,

the neuro ophthalmic models can be viewed in various zoom levels, and rotate it as desired, for comprehensive learning.

ADDITIONAL HIGH-TECH FEATURES IN "EYE MG MAX"

VIRTUAL DISSECTION/SUBSTRATIVE LEARNING

Virtual dissection is a touch-screen table, which provides 3D visualization of anatomy and pathology visualization structures, will be helpful for easy understanding of the concept. It allows to present focused classes with customized content and enhance classroom experience of neophytes. The novices can visualise all the parts of a structure separately (Figure 1). It enable students occupied in Dissection Hall and give them the opportunity to explore individually and learn individually. It gives an opportunity to simulate surgical procedures in an intuitive manner.

DIRECT OPHTHALMOSCOPY EFFECT

Direct ophthalmoscopy is a friend of an ophthalmology postgraduate, helpful in diagnosing various retinal pathologies using a simple and cost-effective technique. This application has become a fruitful companion for postgraduates especially during outreach programmes or camps. Learning this technique with proper and constant training is the key. For novice trainees, it takes some times to accurately identifying the optic disc. Due to the lack of patients, lack of different types of pathologies or the mass crowd in high volume setups, required training does not take place. Another downside of the direct ophthalmoscopy technique is the difficulty in hand coordination using the non-dominant hand. We propose simulative learning for direct ophthalmoscopy at one's finger-tip in their own mobile phone. In this application 'EYE MG Max', we bring in the simulator for direct ophthalmoscopy, with the option to customize for any retinal pathologies, especially to train the hand eye coordination even using the non-dominant

hand (Figure 2). This is an augmented reality module inside the application, wherein the user can select the desired eyeball model with any retinal pathology. The postgraduates have the accessibility at their own fingertip at their free time and use them to train themselves. The eyeball model used in the application uses real-time patient fundus images along with other real-time structures.

SURGICAL SIMULATION

Currently, 3D simulators are not available in a cost-effective manner for simulative learning. We have innovated a novel 3D simulator using eyeball models which are made using real-time patient images, and surgical tools with its microscopic structures giving the ophthalmologist the real-time experience of performing a surgery. This surgical simulator is created in "Eye MG Max" as an application and is customizable and portable. Hand-eye coordination with touch sensation available in this innovation helps in performing surgical and other medical procedures. This application helps in reducing the trouble of carrying a highly stocked wet lab or highly occupying surgical simulators with all the machineries. 3D Surgical and medical simulative training in a cost-effective and accessible way pave the way for future innovations and refine the field of eye care (Figure 3).

PREREQUISITES OF THE "EYE MG MAX" APP AND ITS AVAILABILITY IN VARIOUS PLATFORMS

Augmented reality is a relatively new technology. As a result, certain hardware and software requirements are necessary. The "Eye MG Max" app is available in the latest version of iOS mobile platforms. AR supported in Apple device(iPhone 11 or later) with iOS 13 or later. This app is available free of cost with AR module as subscription pack.

SETTING UP THE FRAMEWORK FOR ACCESSING EYE MG MAX

- Install the “Eye MG Max” app on your iPhone from the App Store.
- Launch the app and select to see either 3D view or AR view

3D View

- Anatomical structure of the eye/cerebral and dural venous sinuses appears.
- Touch and rotate the model in customized degrees or angles for the user’s view of the various structures.
- Move the mobile accordingly to view the structure from the top

AR VIEW

- Launch the app and focus your mobile camera on the plane surface in a well-lit area
- Choose the 3D models as required
- Anatomical structure of the eye/cerebral and dural venous sinuses appears.
- By rotating the mobile phone as well as touching the models, customized degrees or angles for the user’s view of the various structures can be obtained.
- Move the mobile accordingly to view the structure from the top

PEDAGOGICAL AND COUNSELLING TRANSFORMATION

3D models used in the novel application provide real-time experience for understanding the anatomy, pathology and functionality of the neuro ophthalmic structures. The experience of viewing through the Eye MG Max is closer to visualizing the real structures when compared to studying with images. The 3D models simplify this issue by allowing the students to study the models/structures in all 360-degree views and angles so that those studying it with augmented reality can grasp it better. In this application, 3D

models and its functionality is described with proper animations and flow of structure. It is much better when compared to studying with images that are only 2 dimensional where we can only see a single angle/view. These types of tools given real time and practical knowledge compared with other study materials. It is helpful to make their examination easy going with the technical experience.

FUTURISTIC ASPECTS

The use of LiDAR scanned in the "**Eye MG Max"** application, can facilitate the scanning of the external anterior segment of the eye. This includes the cornea, iris, etc. This could help physicians to find some basic information about eyeball of the patient, including the pupil size, iris size, depth of the anterior chamber, etc. This is basic level development using with **LiDAR** scanner in iOS application for scanning and detecting problems in cornea or outer layer of the eyeball. As a result of the research and development, this technology will gradually advance, giving doctors quick access to basic information about the eyeball.

The target audiences for our application are primarily eye hospitals for counseling, students as a supporting material and residents for assisting in their practice. Moreover, we believe this application would be of a huge help for areas of research. In terms of counseling, it would be easier to help patients understand their condition and would improve patient compliance. When the patients are shown a progressive improvement of their condition, they would be even more enthusiastic. For students, they wouldn't have to imagine the structures and they can rather see the structures right before their eyes and learn the complex anatomical structures. This would greatly improve their learning and limit cognitive gaps.

CONCLUSION:

The environment in which we practice ophthalmic medicine has undergone a profound transformation as a result of the COVID-19 pandemic. Innovative methods to teach and learn e-ophthalmology are highly sought after as we adjust to what has become the new "norm" regarding social distance and interpersonal contact. We are confident that this innovative tool in 3D with AR application will significantly impact ophthalmology and its related professions. The introduction of new technologies and techniques in the field of ophthalmology will also improve the cognitive exposure of the neophytes and residents and improve intellectual capacity.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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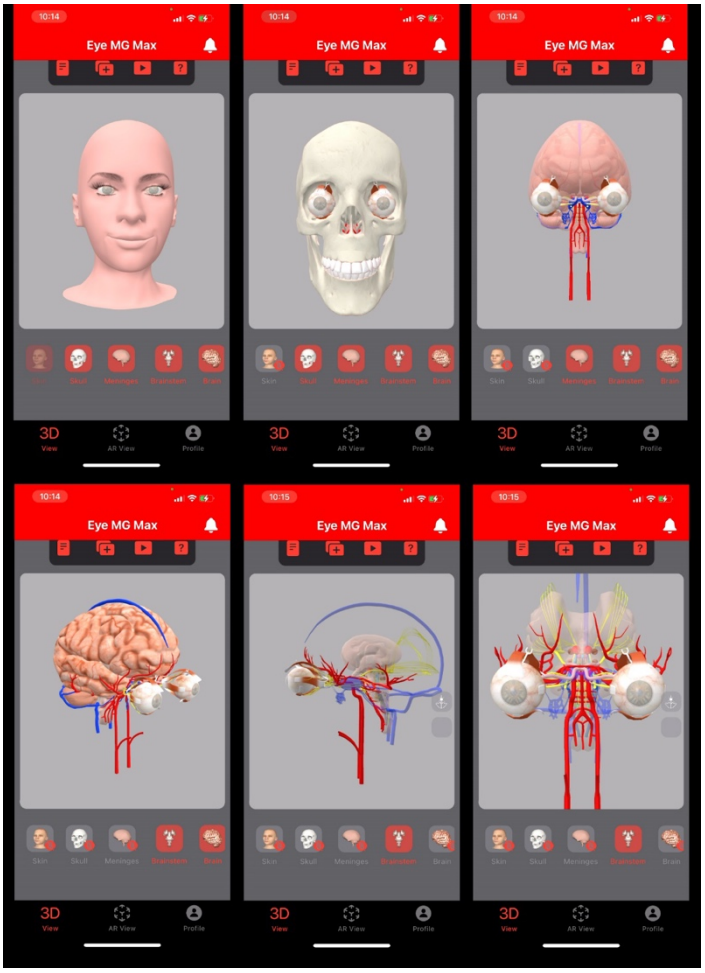
Figure Legends:

Figure 1: The image shows the separated images of a human brain with associated organs



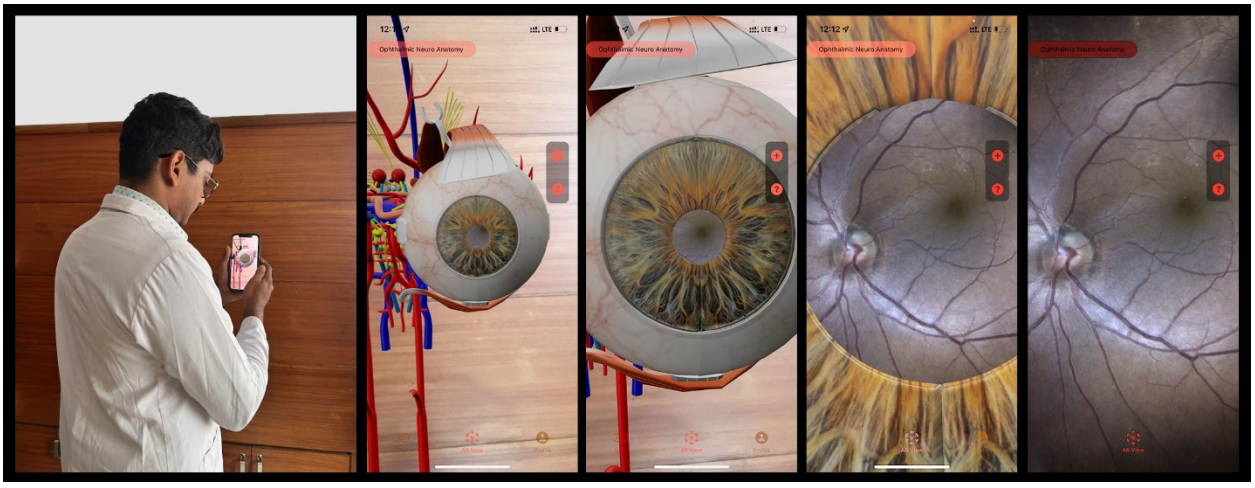
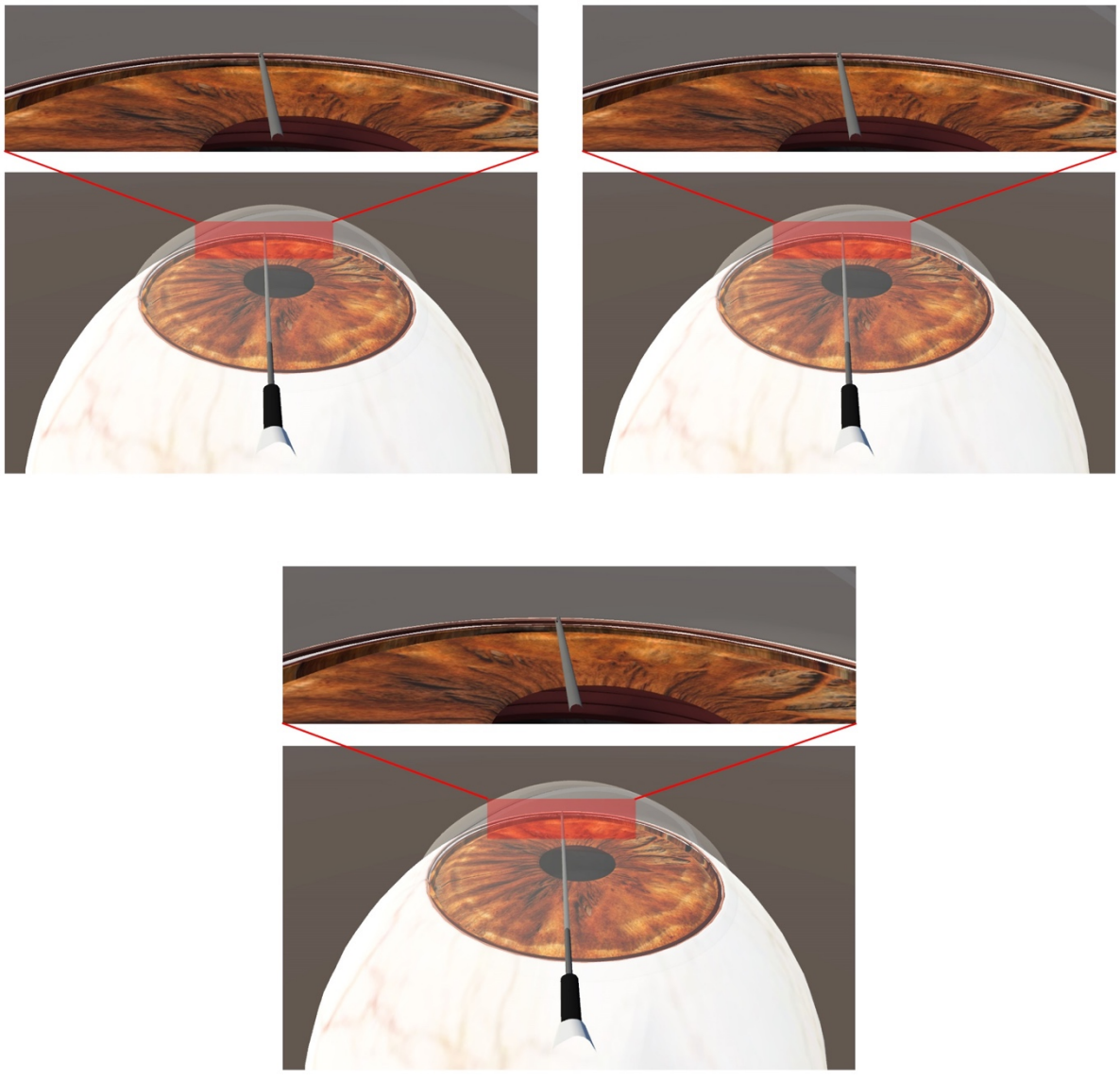


Figure 2: The image shows the direct ophthalmoscopy effect, performing by using "Eye MG Max" application.

Figure 3: The image shows the surgical simulation experiencing by the use of "Eye MG Max" application.



This paper was judged as the BEST PAPER of Ocular Pathology / Ocular Oncology and Tumors Session

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TIME TO DIAGNOSIS" IN NEWLY DIAGNOSED RETINOBLASTOMA: INTERIM ANALYSIS FROM INPOG-RB-19-01

INTRODUCTION

Retinoblastoma (Rb) is the most common intraocular malignant tumour in children. Worldwide, increased awareness about the disease and advances in the management techniques have facilitated early diagnosis and improved survival of these children. Survival rates reported from the Western countries range from 88% in United Kingdom to 93% in United States[1, 2]. In India, Nepal, Africa and South American countries, the prognosis remains poor with increased proportion of these children presenting at an advanced stage of disease. Orbital retinoblastoma has been reported to be 18% in Mexico, 36% in Taiwan and 40% in studies from Nepal [3, 4,5]. Success rate of conservative therapy is dependent on early diagnosis and several studies have been done to identify the factors leading to delayed diagnosis at presentation. Survival from retinoblastoma is dependent on the place of residence and the Global retinoblastoma a study has found that children from low middle income have about 50% three-year survival as compared to almost 100% survival of those from high income countries.[6] Delay in diagnosis in Rb has been associated with higher mortality. Studies from South America have found longer internal between noticing symptoms and

diagnosis was more associated with extraocular disease at presentation[7, 8] . Reduced lag time to diagnosis has been associated with less advanced RB (as per the staging systems) as found in the Swiss study[9]. Studies have also attributed large proportion of delay in diagnosis to delayed referral to specialists[10].

The extent to which prolonged time to diagnosis (TTD) is attributable to delayed presentation by family (Parent lag time) vs delay in the healthcare system (System lag time) is unclear. Study on the time to diagnosis in retinoblastoma patients have been conducted sparingly from India.To understand the concept of delay in diagnosis better , data from the INPOG-RB-19-01 a prospective, multicentric collaborative study aimed at assessing epidemiological, clinical features of RB in India, and to evaluate outcomes following a standardized treatment strategy were analyzed with an objective to understand the TTD and reasons for delay in diagnosis, leading to advanced stage presentation of retinoblastoma in India.

MATERIAL AND METHODS:

A prospective collaborative study was planned and all retinoblastoma treatment centres of the country who maintained a database of treated patients were invited to participate in the study. All participating centres were invited to register newly diagnosed retinoblastoma children identified and treated at their centre. The demographic, clinical, treatment and outcome data were collected for the enrolled patients. The TTD was subdivided into parent-lag time and system-lag time. Epidemiological data inclusive of age, gender, distance from treatment center, state, socio-economic and educational status of parents and family history of RB were recorded. Clinical details documented included stage and laterality. The type and number of healthcare professionals contacted were noted.

This study was registered with the Indian Paediatric Oncology Group (InPOG-RB-19-01). Ethical clearance was obtained. The desired patient-specific information was captured from the routine care and registration database of the hospital and did not involve any patient contact for additional information. Consent was obtained from parents/caregivers at the time of registration at the hospital was considered adequate.

RESULTS:

850 (60% male, 569 patients, mean age 2.5 years, median age 2.1 year) newly diagnosed retinoblastoma children who met the eligibility criteria were enrolled for the study from Aug 2020 till Feb 2023 . 20 centres participated in the study. 68% patients had unilateral disease at presentation. 24.5% of children were less than one year of age at presentation, 65.6% were between 1-5 years age and 10% were more than 5 year of age at presentation. The presenting symptom and the stage at presentation are provided in Table 1 and Table 2. Leukocoria was the most common presenting symptom and 47.68% patients had stage 0 disease at presentation . 14% patients had extraocular disease at presentation and 9% children had metastasis at presentation.

Symptom to diagnosis interval (TTD) was less than 1 month in 59% pf patients(502) and 7.4%(61) patients had TTD of more than 9 months. Parental lag time was less than 3 months in 83.7% of patients (Table 3). The first healthcare provider contacted was an ophthalmologist in 52.8% of patients and paediatrician in 33.3% of patients. Diagnosis was made at the first visit in 62.1% of patients when the first healthcare practitioner consulted was an ophthalmologist whereas in 13.4% of patients who consulted a general practitioner had the diagnosis made at the first consult. The data of the healthcare provider contacted and the proportions diagnosed correctly at the first consult are provided on Table 5.

There was a significant correlation of increased TTD with strabismus as the presenting symptom(P=0.002) , stage at presentation(p<0.05) distance from treating center(P=0.001) and low socio economic status (p<0.05) and negative correlation with improved parental educational status. There was no impact of age, gender, birth order, laterality, family history on TTD.

DISCUSSION

Retinoblastoma is the most common intraocular malignant tumour in children. Timely detection at an early stage can salvage life and eye in these patients. Delayed diagnosis has been associated with advanced stage of disease at presentation in various studies . In India, a major proportion of patients presents at an advanced stage of disease, worsening the prognosis. In the current study, retinoblastoma was extraocular in 14% of patients and metastatic in 9% of patients at presentation, indicating a delay in the diagnosis or treatment initiation. There is a lack of collaborative data from India indicating the reasons and the exact point of delay in diagnosis of retinoblastoma. Stage of presentation is also reported variably in studies from various parts of the country with studies from North India reporting 37% incidence of extraocular retinoblastoma whereas [10] from Southern India Kaliki et al has reported a 9% incidence of extraocular retinoblastoma at presentation[11]. Hence there is a need for collaborative pan India study to have an accurate and validated data available for planning various awareness and education initiatives and interventions aimed at improving the retinoblastoma outcome. The successful take-off of this collaborative study can serve as a major milestone in the direction of prospective collaborative retinoblastoma research in India.

The correct diagnosis was established in majority of the patients in this study within 3 months of diagnosis. Lag time at parental level was less than one month in 51.2% of patients, 1 to 3 months in 32.5% patients and more than

3 months in 17% patients. About one fifth of the family did not seek an early consult despite noticing the symptoms. Lack of awareness about the disease especially in an otherwise asymptomatic young child who is unlikely to have visual complaints might account for the delay at the parent level. Since, early diagnosis and prompt treatment initiation is imperative for improving retinoblastoma outcome, awareness initiatives needs to be directed at the community level to ensure timely initiation of consult by the family for early symptoms.

Increased TTD also had a significant association with socioeconomic status of the patients with lower and upper lower socio economic group having a higher TTD. Strabismus as a presenting symptom was also significantly associated with increased TTD. Tumour involving the macula can cause early reduction of vision causing a sensory strabismus . Since, subtle squint in a child is generally not considered a grave symptom warranting a early medical consult, this can cause disease progression and a delay in the diagnosis. A dilated fundus evaluation hence should be part of evaluation of all children having strabismus and needs to reinforced as part of awareness initiative for healthcare providers.

Diagnosis of retinoblastoma for majority of children in this study were made either by ophthalmologist or paediatrician and a correct diagnosis at the first consult was arrived at by 61% of the ophthalmologists and 55.2 % times by the paediatrician . However, a correct diagnosis was made in only 13% times when the first consult was with general physician. Hence, there is need for strengthening the retinoblastoma awareness initiatives both among the ophthalmologist , paediatricians as well as general physicians. Community awareness programmes should also incorporate these aspects and encourage early consultation with an ophthalmologist or a paediatrician for any ocular symptoms suggestive of retinoblastoma. Once , the diagnosis of

retinoblastoma was established, there was no significant delay in referral and treatment initiation .

20% of children in this cohort had stage 3 or stage 4 disease at presentation. This highlights the needs for advocacy initiatives to incorporate paediatric eye screening, especially for under 5 children during routine healthcare visit like immunization . This will help in early diagnosis of the disease before symptom onset and will help reducing the delay due to parental lag time.

In conclusion, the vast majority of retinoblastoma presented and arrived at a correct diagnosis in < 3months. Whilst this can be optimized there appears to be delayed recognition by the parents. Efforts for earlier diagnosis, therefore, need to be directed towards community awareness and routine screening during contact with healthcare professional such as at immunization. Whether more aggressive biology is at play merits evaluation.

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Table 1: Presenting symptoms of 950 retinoblastoma children

Presenting Symptoms	Count	Percent
LEUCOCORIA	802	84.4%
RED PAINFUL EYE	56	5.9%
POOR VISION	32	3.4%
STRABISMUS	25	2.6%
ASYMPTOMATIC	8	0.8%
ORBITAL CELLULITIS	8	0.8%
Proptosis	7	0.7%
Others	12	1.3%

Table 2 : Stage at presentation of 950 retinoblastoma patients

Staging	Count	Percent
STAGE 0	456	48%
STAGE 1	204	21.5%
STAGE 2	37	3.89%
STAGE 3	119	12.5%
STAGE 4	77	8.1%
Unknown	57	6%

Table 3: Time interval between symptom onset and first consult to any healthcare provider (parental lag) for 950 retinoblastoma children

Table 4 : Time interval between symptom onset and diagnosis of 950 retinoblastoma children

Duration (months)	Count(Percentage)
< 1 Month	487(51.2%)
1-3 Months	309(32.5%)
4-6 Months	86(9.05%)
7-9 Months	25(2.6%)
> 9 Months	43

Symptom to diagnosis Interval	Count(percentage)
< 1 Month	502(52.8%)
1-3 Months	263(27.6%)
4-6 Months	98(10.31%)
7-9 Months	26(2.73%)
> 9 Months	61(6.42%)

Table 5 : Healthcare providers first consulted and proportion of children diagnosed at first consult

Healthcare provider first consulted	Count	Diagnosis at first consult (%)
AYURVEDA/HOMEOPATHIC	9	28.5%
GENERAL PRACTIONER	119	13.4%
OPHTHALMOLOGIST	502	62.1%
PEDIATRICIAN	317	55.2%
PHARMACISTS	3	0%

This paper was judged as the BEST PAPER of Optics / Refraction / Contact Lens Session

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Coimbatore

VISUAL REHABILITATION AND QUALITY OF LIFE WITH CORNEOSCLERAL CONTACT LENS IN IRREGULAR ASTIGMATISM.

ABSTRACT

Purpose: To assess the improvement in visual acuity and quality of life achieved with corneoscleral contact lenses in patients with irregular astigmatism.

Methods: A detailed ophthalmological evaluation followed by selection of first trial lens based on corneal profile and fitting evaluation was done. The lens trial was done for a total of 3 visits, by checking the fitting of the lens for a duration of 8 hours of contact lens wear on each visit and evaluated every 2 hours while in hospital before finally dispensing the lens. Patient satisfaction and wearing time were retrieved using the Contact Lens Impact on Quality of life (CLIQ) questionnaire, given to patient on day 1, 1 month and 6 months to be filled.

Results: Thirty two eyes of 24 patients were analyzed; their ages ranged from 15-60 years. Statistically significant improvements were found in the best corrected vision from before fitting to the visual acuity after fitting ($p<0.001$).The number of visits to achieve correct fit of the lens increased with higher keratometry values. The mean comfortable wear time of the lens

was 10.3 +1.61 hours per day. No statistically significant adverse changes developed in the corneas over this period.

Conclusions: Corneoscleral contact lens will be an effective option, providing a good visual acuity and an optimal visual quality in patients with irregular astigmatism.

INTRODUCTION:

Management of irregular astigmatism possess a great challenge to corneal and refractive surgeons worldwide.[1] Irregular astigmatism produces pronounced visual deterioration and none of the surgical interventions reliably accomplish an ideal visual outcome.[2] Therefore, surgical intervention should be the last option as far as possible. Multiple causes of irregular astigmatism include keratoconus, pellucid marginal degeneration (PMD), post-LASIK ectasia, and irregular corneas following keratoplasty.[2] The rehabilitation of patients with irregular corneas was previously done with lenses such as RGP and Rose K lenses.[3] However, corneas with very high K values (Kmax>70D), these lenses are not well tolerated, hence scleral and corneoscleral lenses(CScL) came in to use. In relation to corneal RGP lenses, CScL and full scleral lenses provide excellent comfort, centration and stability(due to their larger diameter).[4] [5] Scleral contact lens seems to be more effective in irregular corneas than traditional RGP lens since it provides an effective option for correction of residual ametropia and masking surface corneal irregularities with the tear lens between posterior lens surface and anterior corneal surface.[6] [8] [5] However, the scleral lenses are much larger and cumbersome, hence another alternative such as corneoscleral lens have come in to use.[9] CScL have significant advantages in relation to scleral lenses, as they have smaller diameter and they are easier to handle. CScLs, due to a larger optical zone(10), provide more consistent visual performance and greater on-eye stability than corneal

contact lenses. The Scleral Lens Education Society(SLS) classified lenses on the basis of the resting zone area of the lens on the ocular surface. Lenses that are fit to the cornea are to be described as corneal lenses; lenses that rest both on the cornea and the sclera are designated as corneoscleral lenses, and lenses that rest strictly on the sclera are designated as scleral lenses.[11] Within the scleral genre, the smaller end of the spectrum could be termed mini-sclerals and the larger full scleral.[11] [12]

MATERIALS AND METHODS:

A prospective, interventional study was conducted at our hospital between July 2021- July 2022 to assess the improvement in visual acuity and the number of visits taken for correct fit of corneoscleral lenses; to assess quality of life and patient satisfaction using a questionnaire ; to record the complications with corneoscleral use. The institutional ethical committee approval was obtained before commencing the study. The study was carried out in accordance with World Medical Association (WMA)'s Declaration of Helsinki (DoH), 1964 and its subsequent revisions. Informed consent was obtained from the participants. Detailed history was taken and following parameters were recorded which included uncorrected visual acuity; objective refraction followed by subjective refraction and best corrected visual acuity by Snellen visual acuity chart which was converted to log MAR; anterior segment examination by slit lamp; intraocular pressure by non contact tonometry; fundus examination with 90D and examination of peripheral retina with 20D by indirect ophthalmoscopy and complete topographic examination using PENTACAM High Resolution.

According to the inclusion and exclusion criteria's, patients diagnosed with irregular astigmatism was included in the study. Inclusion Criteria were as follows: corneal ectasias, post keratoplasty patients and post refractive surgery ectasias. Patients with ocular surface disorders, media opacities in

the visual axis, who cannot adhere to hygiene standards for handling contact lens and are unable to attend follow up visits were excluded from this study. Selection of first trial lens (base curvature) was done based on corneal profile, following which the lens was gently inserted and fitting evaluation done. Fitting was evaluated twice, firstly after 15 minutes of lens insertion and secondly after minimum of 2 hours. First, the central fit was assessed by checking the vault of lens over the cornea. If the vault of lens over cornea- < 250 microns or if corneal touch is seen, then base curve is steepened or if the vault - >450microns, then flatten the base curve, following which the peripheral fit was assessed by observing lens landing. If there is excessive movement, reduce the landing zone and if there is impingement causing blanching, increase the landing zone.

Then, over the lens acceptance with fogging method was checked for distance and also unilateral near vision noted. Lens fogging or foggy vision after few hours of lens wear was commonly experienced by corneoscleral lens users. Loose landing zone or lens movement is one of the reason. If so, then the landing zone was reduced to L3 or as required. Every trial lens has its unique code imprinted on its convex surface. The code was cross-checked with trial lens label, before finalising the final lens parameters. All the findings, trial lens parameters and over the lens acceptance was mentioned in the fitting assessment sheet to avoid any calculation mistakes. When both central and peripheral fittings were acceptable, over the lens refraction was done and conversion done as per vertex conversion table. This lens trial was generally done for a total of 3 visits, by checking the fitting of the lens for a duration of 8 hours of CScL wear on each visit and evaluated every 2 hours while in hospital. The converted power is added to the trial lens power and the order was placed.

Dispensing is most important aspect of successful lens wear. A healthy tear

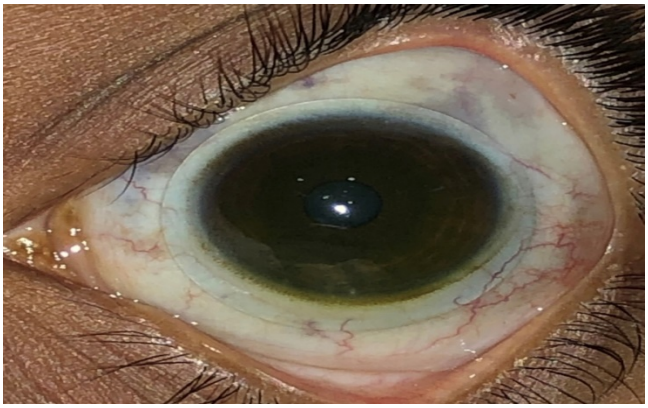
fluid reservoir should be maintained and failure to do so can result in multiple corneal complications. Quality time was given to the users to educate and made to practice multiple times. The trial set should be disinfected after use and at particular interval with cleaning solution to avoid the chances of any eye infection. Patient satisfaction and comfort following corneoscleral lens use on day 1, 1 month and at 6 months was obtained with the help of CLIQ questionnaire.

The sample size was estimated using the formula N= $\frac{Z\alpha 2s2}{d2}$

where N= required/minimum sample size, Zα = 1.96 at 95% confidence level, s = standard deviation , s=1.8 ,d = relative precision, d=10% of mean=15% of 4.3(85% power). This gives a sample size of 31.

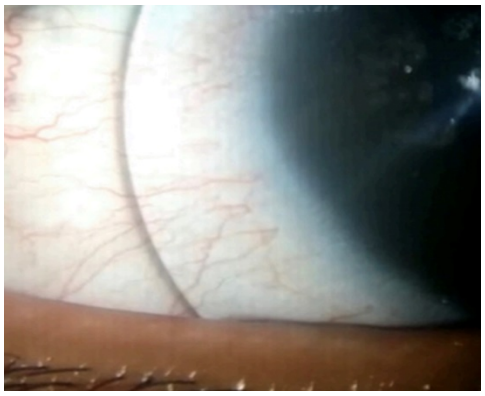
Statistical analysis was done by descriptive statistics. Data were entered in Microsoft Excel version 2016 and were analyzed using a trial version of Statistical Package for the Social Sciences (SPSS) version 23.0. The trial wise comparison was done by ANOVA with Bonferonni t test and Chi-square test was used to find the association. For the test of significance, a p-value of less than 0.05 was considered statistically significant.

Ideal lens landing/peripheral

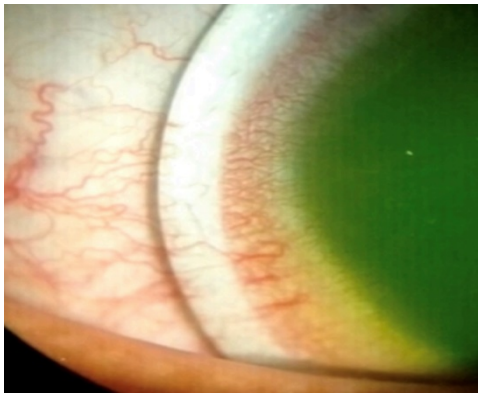


Correct lens

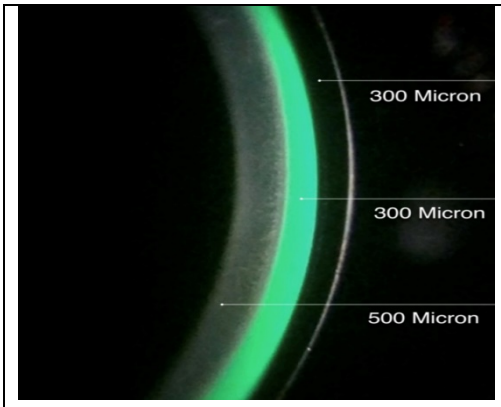
Incorrect lens insertion: conjunctival blanching

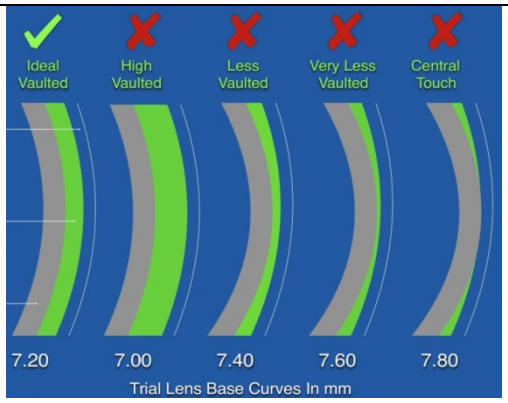


Ideal central fit:



Vault position of lens:





Corneo Scleral Lens Trial Set

Lens Code	7E	7G	7I	7K	7M	7O	7Q	7S	7U	3J	3L	3N	3P	3R
LZ	L7	L7	L7	L7	L7	L7	L7	L7	L7	L3	L3	L3	L3	L3
BC	6.40	6.60	6.80	7.00	7.20	7.40	7.60	7.80	8.00	6.90	7.10	7.30	7.50	7.70
BVP	-12.00	-10.00	-8.00	-8.00	-8.00	-8.00	-8.00	-3.00	-3.00	-8.00	-5.00	-3.00	-2.00	-2.00
DIA	14.50													

RESULTS

32 eyes of 24 patients in the age group of 15-60 years of age having irregular astigmatism were included in the study. 69% were female 31% were male. The mean age of patients was 28.5 ± 8.14 years. Out of 32 eyes, 21(66%) were right eyes and 11 (34%) were left eyes. It took two visits for majority of the eyes 24(75%) to achieve a correct fit of the lens. 3 eyes (9%) and 5 eyes (16%) achieved a correct fit in one visit and three visits respectively.

The mean best corrected visual acuity (BCVA) logMAR was 0.43 ± 0.11, 0.42 ± 0.16 and 0.72 ± 0.21 for those eyes where correct fit of the lens could be achieved in one visit, two visits and three visits respectively. The mean baseline BCVA was 0.50 ± 0.19 logMAR which improved to a mean of 0.14 ± 0.10 logMAR with corneoscleral lens which was statistically significant ($p < 0.001$). Also the p value > 0.05 suggests that the association between keratometric astigmatism and number of visits to achieve a correct fit is not statistically significant. Indications for which corneoscleral lens were fit included Keratoconus (69%), Post Lasik Ectasia(10%), Keratoglobus(6%), Post DALK(6%), Post Penetrating Keratoplasty(6%) and Post Radial Keratotomy(3%). The mean CLIQ raw score was 3.19 ± 0.18, 3.88 ± 0.38 and 4.03 ± 0.56 on day1, 1 month and 6 months of follow-up after corneoscleral lens wear respectively. The CLIQ person measure was 40.65 ± 0.81, 43.52 ± 1.45, 44.04 ± 2.16 for day 1, 1 month and 6 months of follow-up respectively. There was a positive correlation between the total score obtained on day 1 and at the end of 6 months which is statistically significant. Majority (85%) of eyes had no complications, 6% (2 eyes) had a tight fit of the lens after 5 months, 6% (2 eyes) had allergy and 3% (one eye) had tight fit after 1 month. The comfortable wear time ranged from 7 – 12 hours per day with a mean of 10.3 ± 1.61 hours per day.

DISCUSSION

Multiple modes of visual rehabilitation have been proposed in corneal ectasias causing irregular astigmatism. New surgical techniques such as selective zonal ablation, topographic-linked corneal excimer ablation, excimer-laser assisted by sodium hyaluronate and others help to smoothen the cornea and diminish irregular astigmatism but these techniques are difficult and are of limited use in cases of very high astigmatism or insufficient pachymetry.

Various kinds of contact lenses are considered as a unique alternative for the correction of irregular high astigmatism that cannot be corrected with spectacles.

Corneoscleral contact lenses seem to be more effective for visual rehabilitation in irregular corneas since they provide an option for correction of residual ametropia, high-order aberrations and mask surface corneal irregularities with the tear lens between the posterior lens surface and anterior corneal surface. Corneal clearance is the primary advantage of corneoscleral lenses over corneal contact lenses. There is clearly an expanding role of corneoscleral lenses in the management of irregular corneal astigmatism. Fitting of these lenses is relatively easy, have greater oxygen permeability, are very well centered in the eye and usually well tolerated. Corneoscleral lenses provide patients with the optical advantages of rigid gas permeable lenses and the comfort and tolerance approaching those found with soft contact lenses.

In the current study, we assessed the fitting, complications and patient satisfaction with corneoscleral contact lenses in those patients having irregular corneal astigmatism. We recorded the number of visits taken to achieve a correct fit of the lens, examined eyes for any complications during fitting and during 6 months follow up. The mean wear time and patient satisfaction were noted using CLIQ questionnaire on day 1, at 1 month and at 6 months. The age of patients in our study ranged from 15-60 years with a mean age of 28.5 ± 8.14 years, out of which 22 eyes were of female patients and 10 eyes were of male patients. In another study by Waleed Ali Abou Samra et al [2] on corneoscleral lens in irregular astigmatism, the average age was 32.4 ± 10.8 years out of which 20 eyes were of male patients and 16 eyes were of female patients. Cyrielle Suarez et al studied fitting of miniscleral lens in thirty-nine eyes of 23 patients whose mean age was 43 ± 16 years.

Indications for corneoscleral lens in our study were keratoconus (69%), post PK (6%), keratoglobus (6%), DALK (6%), post LASIK ectasia (9%) and radial keratotomy (3%). In the study by Waleed Ali Abou Samra et al,[2] indications were keratoconus (27.8%), post keratoplasty (19.4%), pellucid marginal degeneration (16.7%), post-LASIK ectasia (13.8%), postcorneal rings (11.1%), and corneal injuries (11.1%) for fitting corneoscleral lens. In the study by Cyrielle Suarez et al, indications were keratoconus (46%), post PK (21%), corneal trauma and post refractive surgery (15%) and ocular surface disease (18%).

In the current study, an average of 2.06 ± 0.50 visits were required to achieve a correct fit of the lens. Uncorrected visual acuity (UCVA) and keratometric astigmatism did not show statistically significant association with number of visits but BCVA, average minimum and maximum keratometric values along with average central keratometric values showed statistically significant association with number of visits. In a study by Miguel Romero-Jimenez et al an average of 2.7 ± 0.73 visits (range 2 - 4) were necessary to carry out the semiscleral lens fitting. Cyrielle Suarez et al achieved optimal fit for miniscleral lens in 1 to 3 visits in their study. The number of visits in the current study match with previous reports about fitting scleral lenses and corneal RGP lenses, which states that fitting corneoscleral lenses does not increase the number of visits compared with corneal RGP and semiscleral or miniscleral lenses.

In a study done by Arun K Jain et al on Rose-K contact lens for keratoconus, contact lens fitting was successful in 37 eyes out of 38 eyes. They failed to achieve correct fit in the eye which had an average keratometry of 70.3 D. In the current study, though the mean maximum keratometry was 54.87 ± 7.49 D, we even had a patient whose average central keratometry was as high as 72.2 D for whom a correct fit could be achieved using corneoscleral lens. This

indicates that corneoscleral lenses are a feasible option for even higher keratometric values.

In the current study, the mean UCVA was 1.08 ± 0.26 logMAR, baseline BCVA was 0.50 ± 0.19 logMAR, whereas the mean BCVA with the corneoscleral lens was 0.14 ± 0.10 logMAR which was statistically significant. Other studies Waleed Ali Abou Samra et al [2] and Miguel Romero-Jimenez et al also noted statistically significant improvement in BCVA with Rose K2 XL contact lens. Alipour et al [13] and Cyrielle Suarez et al also reported statistically significant improvement in vision with miniscleral lens in post corneal graft patients and various indications respectively.

Waleed Ali Abou Samra et al[2] reported that 44.45% (16 eyes) discontinued lens wear due to discomfort, cost and handling difficulties. In the current study, all patients were worried about cost of lens and 4 patients (5 eyes) complained of mild discomfort on and off but no patient discontinued wearing the lenses or was lost to follow up. All patients expressed handling difficulties on day 1 but they were comfortable handling the lenses at the end of 6 months. This was probably due to the instructions given to the patients at each visit about the proper way of insertion and removal of their lenses. They were encouraged to use plunger for the insertion and removal of lenses.

Waleed Ali Abou Samra et al [2] reported comfortable wear time of 9.9 ± 2.9 hours per day for corneoscleral lens. Alipour et al [13] reported a mean comfortable wear time of 9.62 hours per day for miniscleral lens in post corneal graft patients. Cyrielle Suarez et al noted the mean duration of wear as 9.2 ± 2.8 hours per day. In the current study, the mean comfortable wear time of the lens by the patients was 10.3 ± 1.61 hours per day (range, 7 - 12). The comfortable wear time in our study was comparable to their studies.

Waleed Ali Abou Samra et al [2] reported allergies (11.11%), tight lens syndrome (11.11%), dry eye syndrome (8.33%) and superficial punctate keratitis (2.78%). Corneal edema, neovascularization, corneal ulcers, or pannus were not recorded throughout their study. In the current study, 85% of eyes had no complications. 3% (1 eye) had tight lens fit at 1 month, 6% (2 eyes) experienced tight lens fit at 5 months and 6% (2 eyes) had an allergic reaction. The fit was reassessed and the lens was replaced for those patients who had tight fit. Two eyes which had allergy were given treatment and they could continue wearing the lens comfortably after treating allergy. No patients had microbial keratitis, corneal edema, neovascularisation or pannus. In the current study, the impact of corneoscleral contact lenses on quality of life in patients with irregular corneal astigmatism was recorded using self-reported results from the CLIQ questionnaire. The average total score that was obtained using the questionnaire on day 1 and at the end of six months showed a positive correlation which was statistically significant and indicated that patients were satisfied using the lens at the end of 6 months.

In the current study, the mean CLIQ raw score on day 1 (3.19), 1 month (3.88) and 6 months (4.03) improved and was statistically significant ($p < 0.001$). Yildiz EH et al [15] did a study to determine the impact of rigid gas permeable and soft silicone- hydrogel contact lenses on the quality of life in keratoconus using CLIQ questionnaire and found the mean CLIQraw score was 3.7± 0.33 in the RGP group and 3.4 ± 0.38 in the soft silicone-hydrogel contact lenses group.

Pesudovs et al [14] reported the mean CLIQperson measure of the healthy contact lens wearers as 51.2 ± 6.2. In the current study, the CLIQperson

measure on day 1, 1 month and 6 months was 40.65 ± 0.81, 43.52 ± 1.45 and 44.04 ± 2.16 respectively. These scores were statistically significant ($p < 0.001$). The lesser mean values in the current study could be related to irregular corneal astigmatism caused by different pathologies. In a study by Mesut Erdurmus et al on contact lens impact on quality of life in patients with keratoconus who wore RGP, hybrid lenses, or soft toric lenses, the mean CLIQ person measure was 45.5 ± 8.2, 45.4 ±7.5 and 48.4 ±10.5 respectively. Yildiz EH et al [15] reported the CLIQperson measure as 42.8 ± 5.5 in the RGP group and 39.6 ± 5.5 in the soft silicone-hydrogel contact lenses for keratoconus.

To the best of our knowledge, no previous studies have assessed the fitting, complications and patient satisfaction with corneoscleral lenses in patients having irregular corneal astigmatism in a sample population in India.

CONCLUSION :

In conclusion, our results state that the use of corneoscleral contact lens will be an effective option, providing a good visual acuity and an optimal visual quality in patients with irregular astigmatism.

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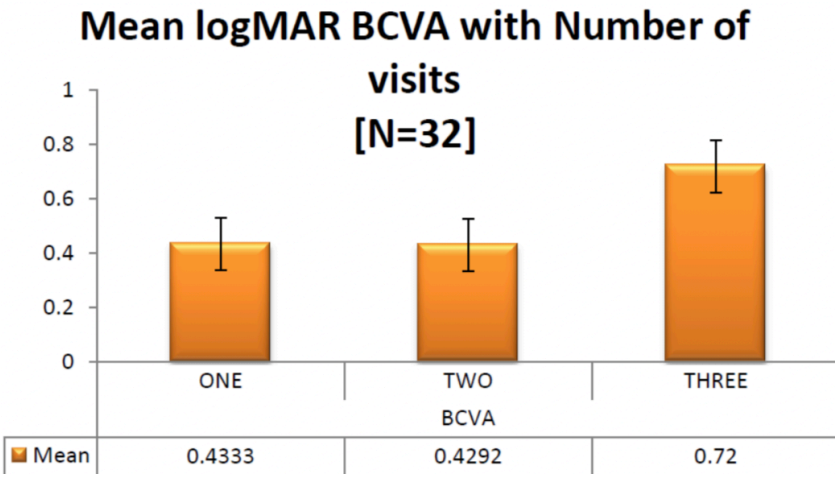
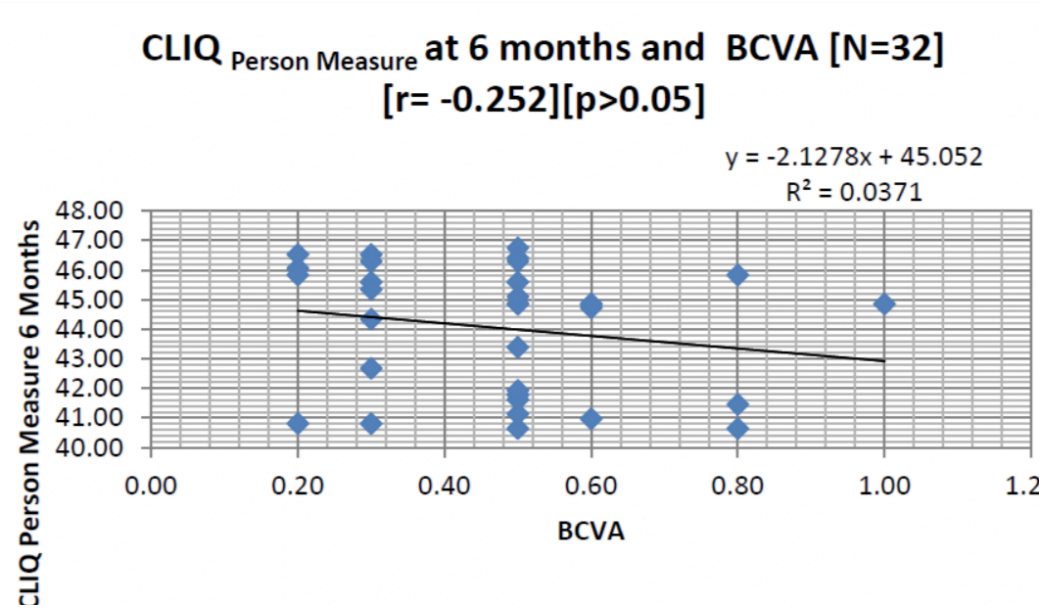
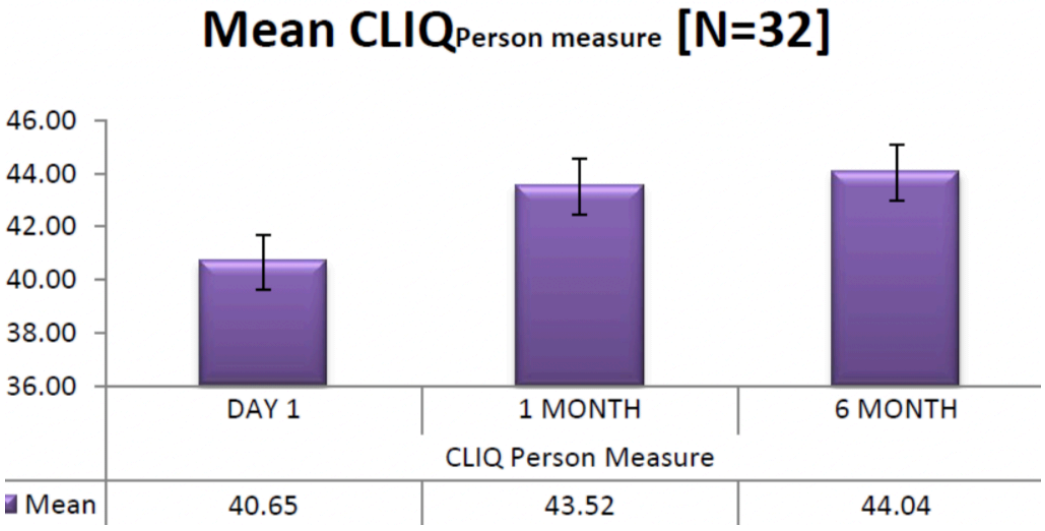
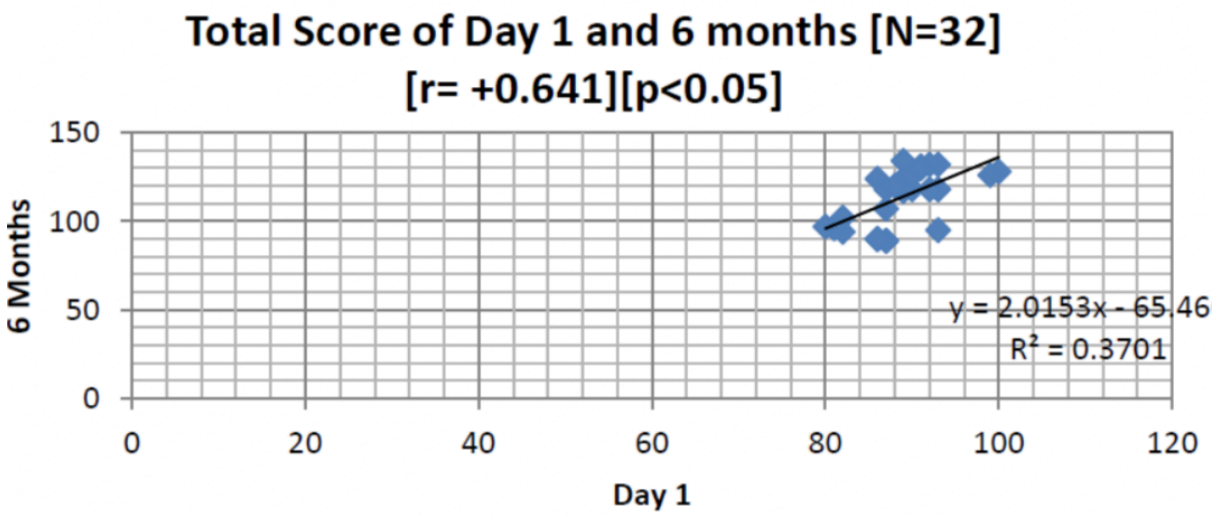
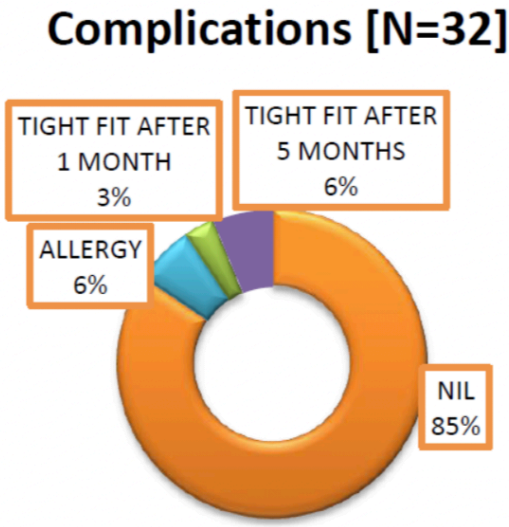



CLIQ Person Measure at 6 months and BCVA [N=32]
[r= -0.252][p>0.05]
y = -2.1278x + 45.052
R² = 0.0371
CLIQ Person Measure 6 Months
48.00
47.00
46.00
45.00
44.00
43.00
42.00
41.00
40.00
0.00
0.20
0.40
0.60
0.80
1.00
1.2
BCVA


Mean CLIQPerson measure [N=32]
46.00
44.00
42.00
40.00
38.00
36.00
DAY 1
1 MONTH
6 MONTH
CLIQ Person Measure
Mean
40.65
43.52
44.04


Total Score of Day 1 and 6 months [N=32]
[r= +0.641][p<0.05]
6 Months
150
100
50
0
0
20
40
60
80
100
120
Day 1
y = 2.0153x - 65.46
R² = 0.3701


Complications [N=32]
TIGHT FIT AFTER 1 MONTH 3%
TIGHT FIT AFTER 5 MONTHS 6%
ALLERGY 6%
NIL 85%

This paper was judged as the BEST PAPER of Orbit & Oculoplasty – I Session

Dr. SAMYA MUJEEB, S22600

Vision Eye Centres, New Delhi

THE SENSATIONAL SURAL – CASE SERIES OF PATIENTS UNDERGOING SURGICAL CORNEAL NEUROTIZATION.

PURPOSE:

To report our practices and outcomes in the treatment of neurotrophic keratitis (NK) through corneal neurotization using sural nerve grafts in multiple age groups.

METHODS:

We conducted a brief review of existing literature on 10 cases of surgical corneal neurotization (SCN) as treatment modality for neurotrophic keratopathy (NK) of various causes. The surgery was performed using the indirect approach and followed up till 18-24 months postoperatively. Corneal sensations and improvement in ocular surface were followed up and noted.

RESULTS:

Outcomes of SCN were beneficial, with negligible complications. Corneal sensation recovery after SCN took almost 3–6 months, while nerve regeneration on confocal microscopy that was monitored in few cases can take as long as 6 months–1 year.

CONCLUSION:

Corneal neurotization is a new stimulating procedure with variable yet satisfactory outcomes in the treatment of neurotrophic keratopathy and can be considered for all age groups at an early-stage disease.

Introduction-

- Corneal Neurotization involves the transfer of a healthy donor nerve segment into a tissue to re-establish either motor or sensory innervation and its principles continue to gain popularity.
- It describes the restoration of structural nerve growth into the cornea to restore corneal sensation and trophic function. Surgical corneal neurotization may be performed either by direct nerve transfer or by using an interpositional nerve graft coapted to a healthy donor nerve.(1)
- Corneal anaesthesia could be caused by-
    - Viral infections
    - Chemical burns, physical injuries
    - Corneal surgery
    - Intracranial tumours and aneurysms,
    - Systemic diseases - diabetes, multiple sclerosis and leprosy .

TYPES OF CORNEAL NEUROTIZATION-

1.Direct nerve transfer-a) contra-lateral(supraorbital and supratrochlear(2),b) ipsilateral and c)endoscopic(3).

2.Indirect/Interpositional nerve transfer- a)sural nerve(ideal, superficial and easy to harvest). b)Greater auricular nerve.

METHODS

- **Study type**- retrospective consecutive case series of patients with NK who underwent corneal neurotization using a sural nerve graft were reviewed .
- **Surgical team**- oculoplastic and corneal surgeon.
- **Number of eyes**-10 eyes of 9 patients with neurotrophic keratopathy of various causes.
- **Follow-up period-**18-24 months postoperatively.
- The corneal sensations and improvement in ocular surface were thoroughly followed up and noted-Tear film height(TFH), Tear break-up time(TBUT),schirmers test, corneal sensations, corneal sheen and corneal reflex.
- Visual acuity was measured pre- and postoperatively. The sensory integrity of the trigeminal nerve in the area of coaptation (forehead) & blink reflex was validated clinically before the procedure manually. Follow-up results were obtained at least 6 months after the procedure.
- Counselling was done & Consent forms were taken pertaining to the prognosis and surgical complications.
- 10 eyes of 9 patients had undergone indirect neurotization, all of them at different stages of follow-up.
- Etiology-

1. Post-traumatic corneal anaesthesia-3eyes
2. Congenital corneal anaesthesia-5 eyes
3. Goldenhaar syndrome-1 eye
4. Idiopathic-1 eye

OUR SURGICAL METHOD-Indirect corneal neurotization with sural nerve transplant.

STAGE 1-HARVESTING THE SURAL NERVE(10-15CMS)-IMAGE ATTACHED

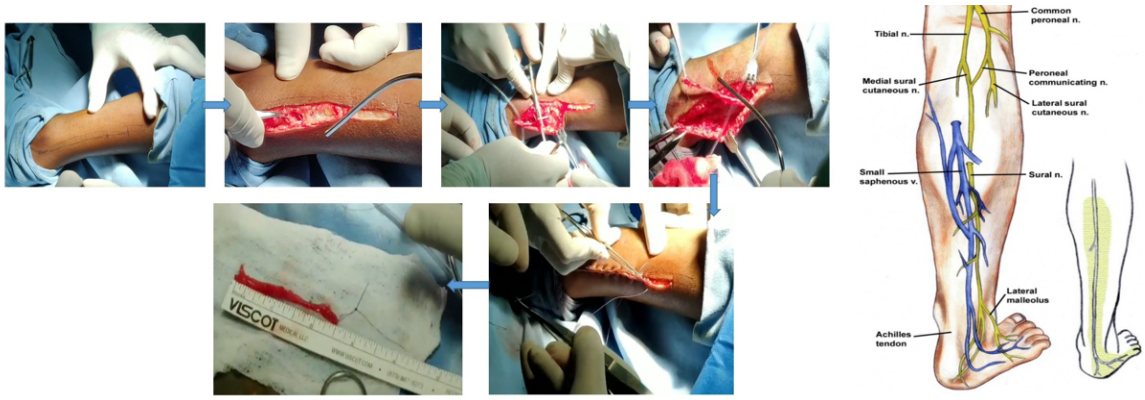
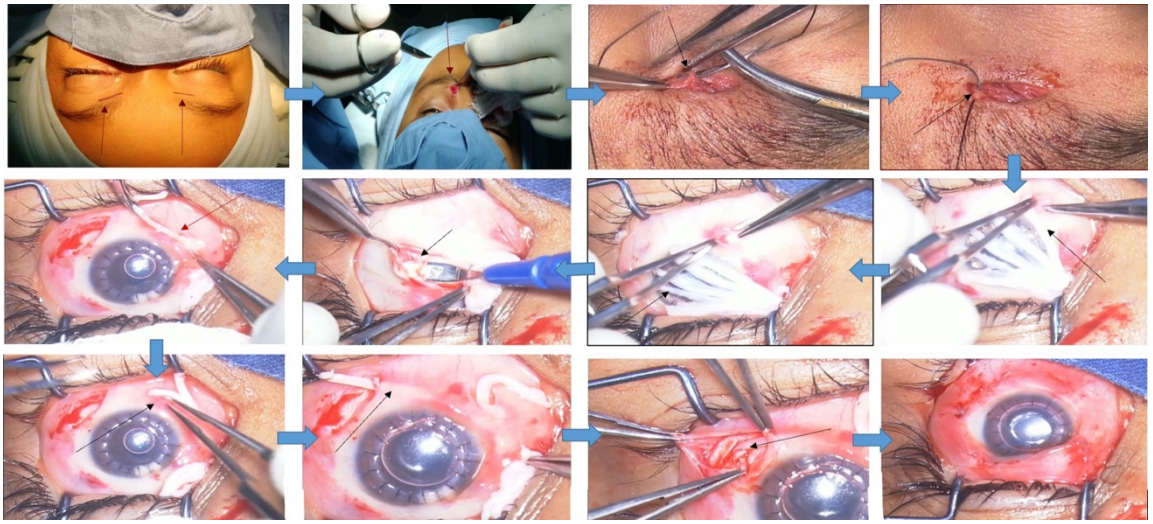


Figure 1-steps of sural nerve harvest from the calf.



STAGE 2-SURAL NERVE ANASTOMOSED TO THE CONTRALATERAL SUPRA-ORBITAL NERVE-IMAGE ATTACHED

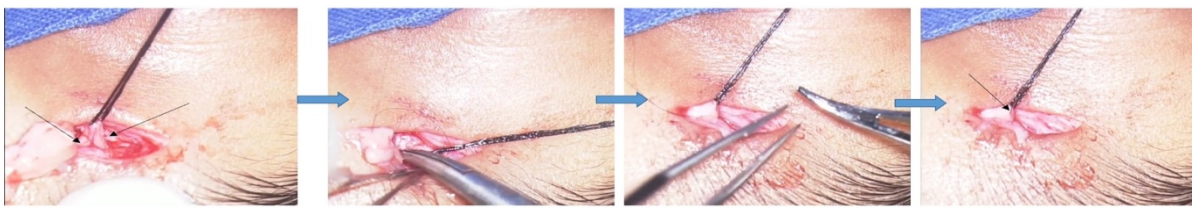


Figure 2- steps of indirect corneal neurotization , where sural nerve is anastomosed to the contralateral supra-orbital nerve, creating 5 fascicles and suturing them to the corneo-sclera tunnels.

RESULTS

Patient Age/gender Year of surgery	Cause of corneal anaesthesia	Corneal neurotization with sural nerve(CN)+/- Other procedure	POST –OP: 1.Corneal sensations 2.C.sheen & surface 3.C.reflex	1.TFH 2.Schirmers 3.TBUT PRE-OP/POST-OP		VISUAL ACUITY PRE-OP/POST-OP	
PATIENT 1 25/F	Post-RTA, 6TH &7THCN.PALSY LE-central corneal opacities	C/L CN- 4 fascicles. Sutured to scleral tunnels.	1.Variable 2.Improving 3.Present -follow up-6months	1.Absent 2. 5mm 3. Absent	1.increased 2. 5mm 3. 3seconds	6/12	6/12
PATIENT 2 26/M	Post-RTA+hemiplegia+ 6th/7th CN.palsy LE-exposure keratopathy.+ Lagophthalmos	C/L CN- 3 fascicles. Sutured to scleral tunnels.	1.Variable 2.Improving-SPKs reduced. 3.Present -follow up-24 months	1.Reduced 2.10mm 3. 3secs	1.Increased 2.10mm 3. 3secs	6/9	6/9
PATIENT 3 10/M	LE-Congenital Corneal Anaesthesia with opacities & vascularization.	C/L DALK+CN - 5 Fascicles Sutured to scleral tunnels.	1.PRESENT 2.Improving 3.Present -follow up-24 months	1.Normal 2.18 mm 3. 5secs	1.normal 2. 20mm 3. 5secs	CF 2mts	CF 2mts
PATIENT 4 8/M	RE-Congenital corneal anaesthesia	C/L CN 3 fascicles. Sutured to scleral tunnels.	1.Absent 2.Improving 3.Present -follow up-2 months	1.Reduced 2.10mm 3.4secs	1.reduced 2.10mm 3.3secs	3/60	3/60
PATIENT 5 4/M	RE-Congenital corneal hypoesthesia syndrome with dense healed ulcer	• PKP+I/L CN+central tarsorrhaphy • 3 fascicles. • Sutured to scleral tunnels close to limbus.	1.variable 2.Improving 3.Present -follow up-24 months	1. Reduced 2. 7mm 3. 2secs	1. Reduced 2. 10mm 3. 2secs	------	-----
PATIENT 6 9/M	BE-Congenital anesthesia syndrome with dense macular opacities	• **RE**-PKP+ I/L CN-Eye lost to traumatic endophthalmitis • **LE**-PKP+I/L CN +lateral tarsorraphy. • 3 fascicles. • Sutured to scleral tunnels	**LE-** 1.PRESENT 2.Improving 3.Present -follow up-24 months	1.Absent 2. 5mm 3. Absent	1. Increased 2. 5mm 3. 2 seconds	RE-PL LE-CF2m	RE-PL LECF2m
PATIENT 7 13/F	RE-Congenital corneal hypoesthesia syndrome with dense healed ulcer	• PKP+AMG+C/L CN • 3 fascicles. • Sutured to scleral tunnels.	1.variable 2.Improving 3.Present -follow up-24 months -no lagophthalmos	1. Reduced 2. 3mm 3. 2secs	1.Reduced 2. 4mm 3. 2secs	3/60	3/60
PATIENT 8 13/M	Goldenhar syndrome LE-Central corneal opacities	I/L CN+Lid reconstruction+CAG+Pannus removal.	1.variable 2.Improving 3.Present -follow up-4 months	1.Reduced 2. 3mm 3. 2secs	1.Reduced 2. 4mm 3. 2secs	RE-PL	RE- HM

- The surgical outcomes of SCN were commendatory and beneficial, with negligible complications.
- Corneal sensation recovery after SCN took almost 3–6 months.

- Nerve regeneration on confocal microscopy that was monitored in few cases can take as long as 6 months, it took 1 year in our cases.(figure 3)
- All the patients had absent pre-operative corneal sensations.
- Extra-ocular muscle movements were the same pre- and post operatively.
- Visual acuity remained unchanged pre and post operatively unless there was a corneal surgery involved.
- 8 eyes showed overall better improvement by 12th month.
- The 2 eyes that were followed beyond 12 months, showed better response with time.
- Patients with Corneo-scleral tunnel showed faster response.
- Younger age group had faster and better response.
- No difference in results between contralateral versus ipsilateral sural nerve transplant.

FASCICLES DETAILS

- 3 fascicles were made in majority (7 eyes)of the cases.
- 4 fascicles in 1 eye(post-Traumatic)
- 5 in 1 eye (neurotrophic keratitis, underwent DALK).
- The TFH,TBUT, Corneal reflex and corneal sheen were found to be improving by the 6th month(except the eye that was excluded due to endophthalmitis), but was seen to improve by the 4th month in the eye with 5 fascicles.
- Corneal sensations significantly improved by the 12th month in 3 of the eyes, and variable response in 4 eyes- fastest improvement improvement seen in the eye with 5 fascicles and corneo-scleral tunnels(3-4th month).

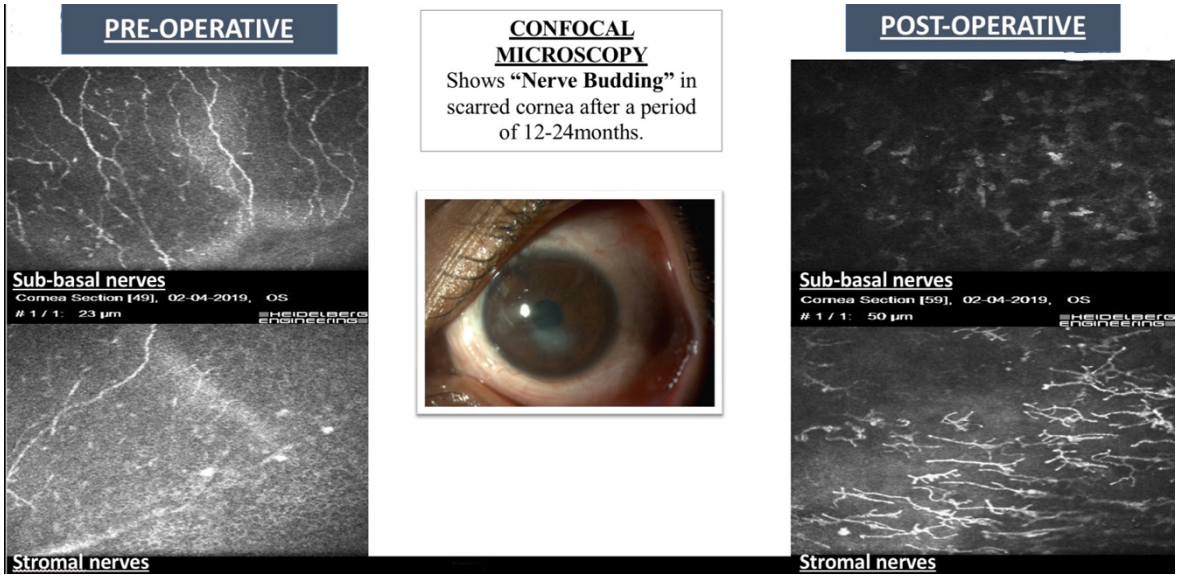


Figure 3- confocal microscopy- pre operative (right side) and post operative (left side).

DISCUSSION

The leading causes of corneal anaesthesia and hypoesthesia include neurotrophic ulcers, impending perforation, chemical burns and secondary infectious keratitis. Non-healing ulcer management consists of extensive preservative-free artificial tears for ocular surface lubrication and topical nerve growth factors. A few temporary surgical measures like conjunctival flaps, tarsorrhaphy and amniotic membrane transplantation are also beneficial.(4) But all these measures are temporary solutions. Proven studies say that lack of corneal innervation reduces the corneo-limbal progenitor stem cell in number and functionality, which can lead to non-healing epithelial defects.

Corneal neurotization surgery is an advanced procedure with a good success rate and prognosis. The transplanted corneal nerves, secrete calcitonin gene-related peptide and Substance P, these substances help in corneal epithelial healing and proliferation. These corneal epithelial cells produce growth

factors and neurotrophins such as nerve growth factor and ciliary neurotrophic factor that accelerate corneal nerve survival.(5,6)

Indirect neurotization with the sural nerve has recently gained popularity due to its easy accessibility and low graft rejection rate.(7) Indirect neurotizations utilize coaptations via an end-to-end, or end-to-side approach, we adopted the end-to-side technique.

Literature states, complete neurotization of the central cornea may be seen from 6-24 months post-operatively, and success is also limited by the patient's age and comorbidities. (8) Few of our patients revealed new nerve budding after 12 months and younger patients had a better chance of nerve growth.

Follow-up was planned as follows: day 1, week 1, 3,6,12,24 months. At follow-up, subjective and objective measures of corneal sensation were assessed. Confocal microscopy is a good objective measure of corneal re-innervation for follow-up.(9)

Patients were evaluated for new or recurrent punctate epithelial erosions, epithelial defects, ulceration, neovascularization, scarring, corneal melt and perforation, and/or denervation. We lost a few patients in the follow-up period and a few of them are still ongoing in the follow-up period. The only limitation of our study was the unavailability of a corneal aesthesiometer, as the variations in corneal sensations could have been better monitored and compared to the pre-operative levels.

In this study, although the degree to which corneal sensibility is restored varies, the overall outcome and aggregate results show significant improvement in the overall ocular surface health from pre-operative states.

CONCLUSIONS

- Corneal neurotization is a promising procedure with variable yet satisfactory outcomes in the treatment of Corneal anaesthesia.

- Corneal transplant & other lid procedures can be combined with Corneal neurotization.
- Along with the reappearance of Corneal sensations, improvement of the ocular surface can be considered a successful outcome.

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This paper was judged as the BEST PAPER of Orbit & Oculoplasty – II Session

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TRANS CONJUNCTIVAL INTRA-LEVATOR TRIAMCINOLONE FOR UPPERLID RETRACTION IN THYROID EYE DISEASE

PURPOSE:

To evaluate the role of transconjunctival intra-levator injection of triamcinolone acetonide (TA) in upper eyelid retraction in thyroid eye disease (TED).

METHODS:

Retrospective interventional case series of 37 eyes of 22 patients who underwent transconjunctival TA injection (40 mg/mL) into the levator palpebrae superioris (LPS) muscle for TED-related upper eyelid retraction between January 2019 to November 2022.

Results: Mean age was 45.7 years and 13(59.1%) were females. Bilaterality was seen in 13(59.1%)cases. Fourteen(63.6%) were hyperthyroid,6(27.3%) were hypothyroid and 2(9.1%) were euthyroid. Disease was active in 12(54.5%) and inactive in 10(45.4%) cases. Pre-treatment Margin-Reflex Distance (MRD) 1 was 6.0± 1.9 (range, 03-13) mm. The mean number of TA injections was 1.77 ± 0.97 (range, 1-4) with mean average dose of 23.7 ± 5.1 mg. Time to maximal response was a mean of 37.6 weeks. At a mean follow-up of 16.3 months, MRD1 was 4.5 ± 1.5 (range, 02-10) mm, showing improvement in all cases. Mean reduction in MRD1 was 1.5 ± 1.6 mm

(p=0.000).Mean reduction in palpebral fissure height, superior scleral show and lagophthalmos was also statistically significant. There was no significant regression from maximal response. Only 1(4.5%) patient showed increased intraocular pressure on follow-up visit. There was no significant difference in number of injections, dose of TA required and maximal response seen in active and inactive TED cases.

Conclusion: Transconjunctival TA injection to LPS muscle is an effective treatment option for TED-related upper eyelid retraction.

Keywords: Thyroid eye disease; Eyelid retraction; Triamcinolone acetonide; Levator palpebrae superioris

INTRODUCTION

Thyroid eye disease(TED) is the most common disease affecting the orbit. It is a complex, autoimmune condition caused by activation of orbital fibroblasts by autoantibodies directed against thyroid receptors. This leads to inflammation and expansive congestion of orbital fat, extraocular muscles and periocular structures leading to tissue remodelling.[1] Clinical presentation of TED is heterogenous. The association with systemic thyroid status can also vary. It can precede, follow or present concurrently with dysthyroid status.[2] The natural course of the disease shows an initial active phase of inflammation, a plateau phase of stabilisation and the final phase of inactivity wherein the facial changes set in often show incomplete remission.[3]

Upper eyelid retraction is a characteristic and most common sign of TED. Clinically it can lead to lagophthalmos and exposure keratopath.

Various surgical and medical options have been used for the treatment of lid retraction in TED. Surgical options are irreversible, invasive and can be used only when the disease is inactive. Often they are reserved as a last resort in these cases. Medical treatment includes treatment of underlying dysthyroid

status, treatment with oral or systemic steroids and immunomodulators. The anti-inflammatory action of triamcinolone acetonide can be utilised for the treatment of lid retraction in TED especially in active phase where other options do not seem to work well.

Herein we present the role of transconjunctival intra-levator injection of triamcinolone acetonide (TA) in TED.

MATERIALS AND METHODS

This was an interventional retrospective study between January 2019 and November 2022. The study group included 37 eyes of 22 patients seen during the period. The patients seen fit into the following inclusion criteria: mild to moderate TED, active or inactive disease status, unilateral or bilateral lid retraction, age 18 years or older, absence of other systemic disease, absence of severe ocular motility restriction, severe proptosis, optic neuropathy or corneal ulcer.

All patients were informed in details about the various options available, the benefits and possible side effects of local triamcinolone acetonide steroid injection. Informed consent was obtained from all patients. Detailed ophthalmologic examination was done in all cases which included best-corrected visual acuity, baseline intraocular pressure using a Perkins tonometer, pupillary reflexes, ocular motility and fundoscopy. Proptosis was measured with Hertle's exophthalmometer. Measurement of palpebral fissure height(PFH), margin reflex distance 1 (MRD1), lagophthalmos and scleral show was done in all cases. Photographic documentation was done prior to the treatment in all cases.

Treatment was done in out-patient room under topical anesthesia. Triamcinolone acetonide(40mg /mL) was injected in subconjunctival area on lid eversion. Patients were followed up at 1, 2,3, 6 months and 1 year or more wherein at each visit similar measurements and photographic

documentation was taken along with intraocular pressure measurement. Statistical analysis was performed using SPSS (SPSS Inc, Chicago,IL).

RESULTS

The mean age of patients in the study population was 45.77+/- 11.18 (range,31 to 67 years) years. Nine(40.9%) were males and 13(59.1%) were females. Fourteen(63.6%) patients had hyperthyroidism,6(27.3%) had hypothyroidism and 2 (9.1%) were euthyroid. The disease was active in 6(27.3%) and inactive in 16 (72.7%) patients. Bilaterality was seen in 13(59.1%) cases. The mean number of TA injections administered were 1.77+/- 0.97 (range, 1-4). Mean average dose was 23.7+/-5.1 mg(range, 18-40 mg).

Pre-treatment mean measurement of margin reflex distance 1 (MRD1) was 6.0± 1.9 (range, 03-13 mm),palpebral fissure height (PFH) was 13.54 ± 3.071 (range, 10 – 23 mm), superior scleral show was 1.73 ± 1.66, and lagophthalmos was 1.03 ± 1.63 (range, 0-6 mm).Time to maximal response was mean of 37.6 weeks. At a mean follow up of 16.3 months mean MRD1 was 4.5 ± 1.5 (range, 02-10) mm, showing improvement in all cases. Measured value of post-treatment PFH was 11.86 ± 2.5 (02- 06 mm), superior scleral show was 0.229 ± 0.47, and lagophthalmos was 0.443 ± 1.08 (0- 5 mm).The mean reduction in measurements in all cases was statistically significant (p value <0.001). Mean reduction seen in MRD1 was 1.5 ± 1.6 mm (p<0.001). No significant regression from maximal response was seen. Only 1(4.5%) patient showed increased intraocular pressure on follow-up visit.

DISCUSSION

Lid retraction is the most common signs of TED. Clinically it can cause lagophthalmos and exposure keratopathy warranting immediate treatment. Additionally, patients with upper lid retraction are frequently concerned with the change in the physical appearance affecting their quality of life.[4]

Options for management of lid retraction in TED depends on stage of the disease. Surgical options are irreversible, can be used in inactive stage and hence kept as the last resort. Non-surgical modalities can be used as successful alternatives in these cases. The advantages include ease of administration on an outpatient clinical setting, less morbidity, less recovery time and early results. Non-surgical options include use of botulinum toxin but the effect is temporary, unpredictable and the procedure is costly.[5,6] Similarly use of fillers like hyaluronic acid(HA) although relatively safer can be unpredictable because of variability in HA distribution in the eyelid plane.[7,8,9]

The systemic use of steroids is a well-established modality of treatment of TED which leads to reduction in active inflammation and relief of symptoms. Recent studies have shown encouraging results of local TA injection for upper lid retraction in TED. A large case series by Lee et al. showed successful treatment in 75% of the treatment group on last follow-up versus 57% in untreated group.[10] This study also studied the effect of TA injection in active and inactive phase of TED. Better results were seen in active phase of the disease. In group with active phase mean decrease in MRD1 was 1.1 mm versus 0.56 mm in inactive phase.[10] In our study group a statistically significant improvement was seen in both active and inactive phase of the disease. (Image 1 and 2)

We saw a mean reduction of 1.5 mm in MRD1 in our study, which was statistically significant (p value <0.001). The measured values of PFH, scleral show and lagophthalmos showed a statistically significant decrease as well in all cases.(Table 1) Range of number of injections was 1 to maximum 4.The

injection could be effectively administered and showed good results in both active (12, 54.5%) and inactive phase (10,45.4%) of TED. The measured value of correction of upper lid retraction was stable at a mean follow-up of 16.3 months in our study with no regression from maximal response.

The etiology suggested for lid retraction in TED are multifactorial and complex. Mechanisms proposed include increased sympathetic tone of Muller's muscle, levator muscle fibre enlargement, levator muscle fibrosis leading to contracture, levator overaction from the fixation duress in overcoming inferior rectus restriction, fatty infiltration and degenerative changes in muscle and connective tissue proliferation forming adhesion between levator and adjacent structures. Inflammatory changes in the muscle is a well-known and well studies mechanism.[11,12,13,14,15] Mechanisms proposed for the effect of TA in lid retraction is anti-inflammatory and anti-fibrotic effect. It has also been proposed that steroids can cause myopathic ptosis. It can detach the levator aponeurosis from the tarsal plate causing aponeurotic ptosis. Steroids can reduce edema thus reducing SR-LPS diameter causing improvement of retraction. Targeting the inflammation during active phase before chronicity and fibrotic remodelling sets in can help achieve better results. TA does not address all possible mechanisms of lid retraction, but is a highly effective treatment option in active and inactive stage of the disease for lid retraction as was seen in our study thus avoiding the need for surgical correction.

Glaucoma is a relative contraindication for use of TA. Xu et al. reported IOP rise in 4 of 21 patients in their group.[16]Although the rise of IOP was seen in only one of our patient in the study group, careful IOP follow-up is mandated. The patient was treated with topical anti-glaucoma medication and the IOP could be kept under control.

CONCLUSION

TED is a complex challenging disease. TA injection is an effective alternative to surgical procedures for upper lid retraction but due to the heterogenous nature of TED the case selection should be proper and the treatment must be tailor made for a given patient for best outcome. The subconjunctival administration of TA has shown promising results in our study group and is an established method of treatment of lid retraction in our armamentarium for management of TED.

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Table 1: Mean measured values before and after treatment

	Pre-treatment	Post-treatment	P value
MRD1	6.0± 1.9 (03-13 mm)	4.5 ± 1.06 (02-10) mm	<0.001
PFH	13.54 ± 3.071 (10 – 23 mm)	11.86 ± 2.5 (02- 06 mm)	<0.001
Superior scleral show	1.73 ± 1.66	0.229 ± 0.47	<0.001
Lagophthalmos	1.03 ± 1.63 (0-6 mm)	.443 ± 1.08 (0- 5 mm)	<0.001

LEGENDS:

Image 1: Improvement in upper eyelid retraction in a patient with active thyroid eye disease a) Before treatment; b) After 2 injections of triamcinolone acetonide

Image 2 : Improvement in upper eyelid retraction in a patient with inactive thyroid eye disease. a) Before treatment; b) After 1 injection of triamcinolone acetonide

Image 1 :

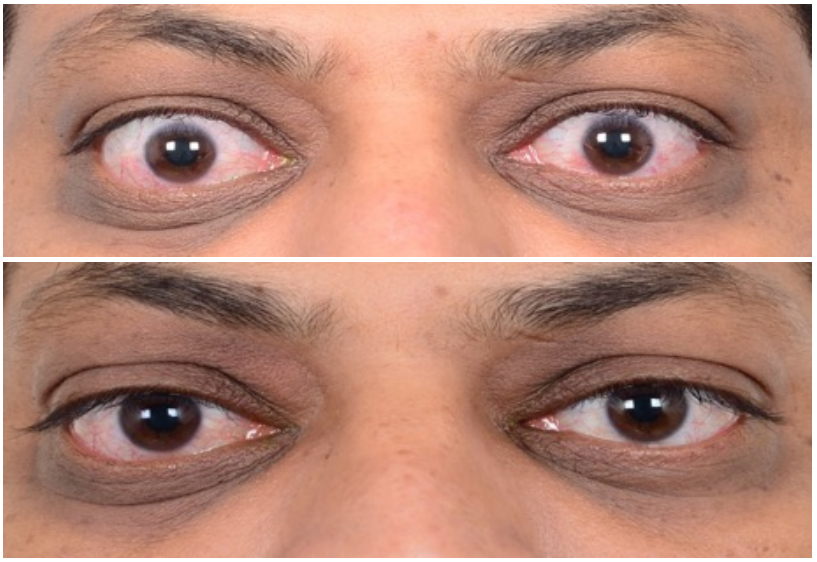
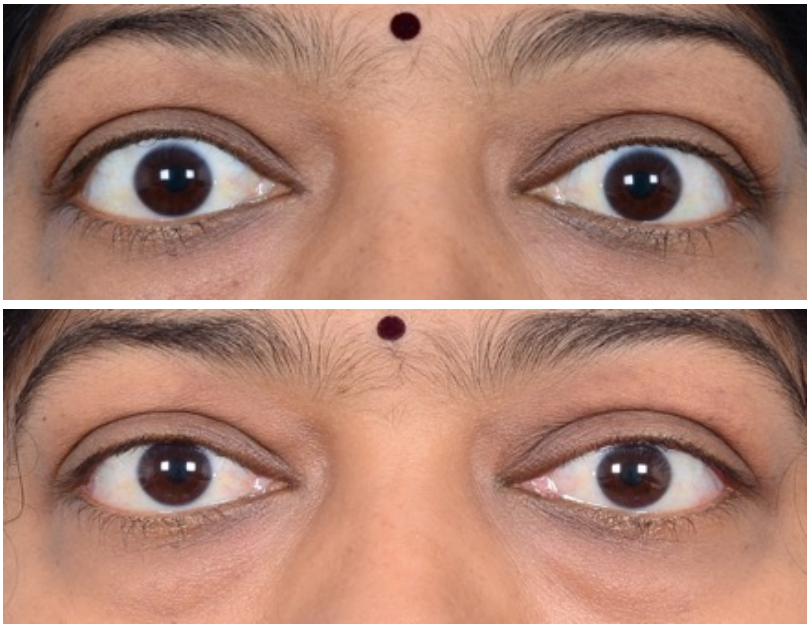


Image 2:



This paper was judged as the BEST PAPER of Pediatric – I Session

DR. VIBHA BADRINATH V24701

Sankara Nethralaya
Chennai

IOL FORMULA CALCULATION IN PAEDIATRIC EYES- DO WE HAVE AN ANSWER?

ABSTRACT

Aim:

To compare the predictability of SRK II and Barrett's Universal II formulae in paediatric eyes and possible effect of axial length, keratometry and age.

Methods: Retrospective analysis of children<8 years who underwent cataract surgery with intra ocular lens implantation between September 2018 & July 2019. The prediction error(PE) of SRK II and Barrett's was calculated & compared.

Results:72 eyes of 39 patients were included. In eyes with axial length between 18-21mm the PE(1.37±1.45) for Barrett's was higher than the PE(-0.06 +/- 0.95) for SRK II but vice-versa for the 21-24mm group. Barrett's performed better in eyes with a K ≤ 45 D and showed a smaller PE across all age groups, especially in children <2 years and >5 years of age. Overall, Barrett's formula gave a lower mean PE as compared to SRK II (p <0.05).

CONCLUSION:

Barrett's formula shows predictable outcomes in children <2 years & >5 years of age, in eyes with axial length between 21 mm and 24 mm & with flatter corneas.

INTRODUCTION

Intraocular lens implantation in paediatric cataract surgeries is now being routinely performed by ophthalmologists worldwide. The major challenge here lies in the IOL power calculation. Factors that need to be considered are the tendency for myopic shift and the axial growth of the eyeball in children for which a planned hyperopic under correction is needed. Also, calculation of ocular parameters such as axial length, keratometry, etc are difficult in children due to poor cooperation. In very young children these measurements must be done under general anaesthesia where proper centration is not possible for accurate values. Lastly, the various IOL power calculation formulae that are available are validated in adult eyes, their accuracy in paediatric eyes is still unclear.

The aim of our study was to assess the predictability of the Sanders-Retzlaff-Kraff II(SRK II) and the Barrett's Universal formula and the possible effect of axial length, keratometry and age.

MATERIALS AND METHODS

A retrospective analysis of the children under 8 years of age who underwent cataract surgery with intraocular lens implantation under general anaesthesia from September 2018 to July 2019 was performed. The surgeries were performed by 5 surgeons. A total of 123 patient records were analysed and 72 eyes were included in the study. Others were excluded due to other ocular anomalies like persistent foetal vasculature, lenticonus, coloboma, peter's anomaly or other ocular disorders like glaucoma, retinal detachment, or trauma.

After induction of general anaesthesia, a detailed examination under anaesthesia was performed in all cases. The keratometry readings were recorded using a Nidek KM 500 handheld keratometer (Nidek, Inc, remont, CA) with good centration on the cornea. An average of 3 readings were taken. Thereafter the intraocular pressure was recorded using Perkin's applanation tonometer. The biometry including axial length, lens thickness and anterior chamber depth was then performed using immersion technique (OcuScan RxP, Alcon laboratories, Inc, Fort Worth, Tx). The axial length was recorded till 10 readings with sharp retinal spike followed by low orbital spikes were obtained. An average of these readings was taken. Similarly, the anterior chamber depth and lens thickness were recorded. The intraocular lens power was calculated using the SRK II formula using an age-appropriate target hypermetropia according to the Enyedi's rule of seven .

The surgeries were performed by experienced surgeons with an experience of >10 years using a standard technique. Post operatively antibiotic and a tapering dose of steroid drops were given and patients were evaluated on post op day 1, day 2, day 3, 1 week and then 1 month. Refraction was performed on day 3 post operatively and glasses or contact lenses prescribed. Refraction was again performed at the 1 month follow up visit. The refraction noted between 1-3 months post operatively was used to calculate the spherical equivalent in the study.

The prediction error of SRK II formula was thus calculated by subtracting the target refraction and the actual post-operative spherical equivalent. The preoperative biometry values were then used to calculate the IOL power by Barrett's universal II formula with the same target refraction as used in SRK II. The predicted spherical equivalent of Barrett's formula was then back-calculated using the SRK II formula with the IOL power obtained with Barrett's formula. The difference between the target refraction and this back

calculated spherical equivalent was the back calculated prediction error for Barrett's formula. The mean prediction error (PE) and mean absolute prediction error (APE) were calculated individually for each of the two formula and in various study groups. The difference in the prediction error of postoperative refraction between the two formulas was then calculated for significance. Subgroup analysis was done by dividing the study sample based on axial length, keratometry values and age.

Statistical analysis was performed using SPSS software (version 21.0, SPSS, Inc.). The differences in prediction error and mean absolute prediction error in postoperative refraction between the formulas were assessed by post-hoc analysis by Wilcoxon Signed-Rank test. P value less than 0.05 was considered significant.

RESULTS

72 eyes of 39 patients were included in the study. The mean age at surgery was 3.8+/- 2 years. The mean axial length was 22.1+/- 1.5mm and the mean keratometry was 44.7+/- 1.7 Dioptres. For data analysis we divided subjects into 3 main groups based on age, axial length and keratometry. (Table 1)

In our cohort we found that the Barrett's formula gave a lower mean prediction error of 0.094 ± 1.41 D as compared to SRK II PE -0.60 ± 1.11 (p value <0.05). There was no statistically significant difference (p=0.6) between the mean absolute prediction error of SRK-II (0.97 ± 0.81) and Barrett's (0.95 ± 1.04).

There was significant difference in the prediction errors using the SRK-II formula (p=0.007) across the subgroups of axial length. Across the subgroups, there was significant difference in the prediction error(p=0) as well as the absolute prediction error (p=0.008), while using the Barrett's formula.

While the overall average PE using the SRK-II and Barrett's formula was comparable, in eyes with axial length between 18-21 mm, the PE (1.37±1.45) and APE for Barrett's (1.5± 1.31) was higher than the PE (-0.06 ± 0.95) and APE (0.75±0.56) for SRK II (Table 2).

There was significant difference in prediction errors using SRK II formula (p =0.013) across the subgroups of keratometry. The PE (0.04±1.15) and APE (0.79+/-0.83) for Barrett's was lower compared to the PE (-0.90±1.04) and APE (1.04±0.91) for SRK II in eyes with a keratometry ≤ 45 Dioptres.(Table 3)

Across the age groups there was significant difference in prediction error (p=0.02) and absolute prediction error (p= 0.017) using SRK II formula with the prediction error being the maximum (-0.99±1.29) in the age group between 3 years to 5 years and least (-0.15±0.84) in the age group ≤ 2 years. Barrett's formula showed a smaller prediction error of 0.09±1.41 in the overall group and was lesser across all ranges of age group when compared with SRK-II.(Table 4)

SUB-GROUP ANALYSIS

Prediction Error and Axial Length

There was a significant negative correlation between the mean prediction error and the axial length across the subgroups using the SRK II formula and the Barrett's formula.

The >24 mm axial length group showed a significant strong positive correlation (Pearson correlation coefficient r= 0.93, p=0) on comparison of the mean absolute prediction errors using the SRK-II formula. (Table 5). When the mean PE were compared in the >24 mm axial length group, there was a significant negative correlation (r = -0.82, p <0.00) of post-operative refraction using Barrett's formula. (Table 5).

Prediction Error and Keratometry

We found a strong significant negative correlation between the mean prediction error in the overall keratometry group using the Barrett's formula ($r = -0.72$, $p < 0.000$) and a significant but weak positive correlation ($r=o.3$, $p=0.01$) using the SRK-II formula. (Table 6)

Prediction Error and Age

There were no significant correlations between age and the refractive accuracy using the two formulae in any of the subgroups of age. (Table 7)

DISCUSSION

The choice of IOL power formulae following cataract surgery is most important in determining a satisfactory visual outcome. More so, in paediatric cataract surgery due to the large unpredictability of its outcome. Standardisation of target refraction following cataract surgery according to age has been done by Enyedi et al1 and has been validated by Sachdeva et al Our study aimed to compare the predictability of the SRK-II and Barrett's formula for IOL power calculation and the influence of axial length, keratometry and age on the prediction error.

In our cohort we found that the Barrett's formula gave the lowest mean prediction error of (0.094 ± 1.41 D) as compared to SRK II (PE -0.60 ± 1.11) (p value 0.00). However, the mean absolute prediction errors were similar (SRK II 0.97±0.81, Barrett's 0.95±1.04) and there was no statistically significant difference (p value 0.6).

For further subgroup analysis, we divided our cohort into categories as mentioned in table 1.

In our cohort, SRK -II has shown predictable results in the those with axial length between 18-21mm and Barrett's formula gives a lower prediction error in eyes between 21 mm to 24 mm. In longer eyes (>24mm), both the

formulae give a comparable and higher prediction error. But according to a study by Kane et al , in eyes with an AL longer than 22.0 mm, the Barrett Universal II formula was a more accurate predictor of actual postoperative refraction than the other formulas.

For steeper corneas of > 45D, the SRK II and Barrett's formulae had predictable results as against the flat corneas ⍰ 45 D where only Barrett's had predictable outcomes. There was a strong significant negative correlation of -0.73 (p=0) between the keratometry and prediction errors using Barrett's formula.

Barrett's formula showed a smaller prediction error of 0.09⍰1.41 across all subgroups of age, especially <2 years and > 5 years age groups when compared with SRK-II. A study by Chang et al compared prediction errors of 8 IOL power formulae in children which showed that SRK-T was relatively accurate in children aged less than 2 years and Barrett's and Haigis formulae fared better for children older than 2 years. They reported that for smaller eyes (AXL < 21mm) Hoffer-Q and SRK-T had the most predictable outcomes. A more recent study done by Eppley et al in children ≤ 16 years of age has shown Barrett's to have lowest mean PE (-0.22D), median PE (-0.26D) and median APE (0.71) compared to the other formulas. Holladay II performed similarly to Barrett, and SRK-T had the greatest mean PE (-0.50D). Barrett predictions were stable across all variables like axial length, age, biometry type and keratometry.

Kekunnaya and associates have compared the prediction errors in children aged under 2 years, with SRK II, SRK-T, Holladay, and Hoffer Q formulae. They have reported that SRK II gives predictable results as compared to the other three. Further the same group has also reported that axial length and keratometry influence prediction errors with the Holladay, Hoffer Q and the SRK-T. Prediction errors tended to be high with flat corneas and the SRK T. In

our cohort Barrett's gave predictable results in flatter corneas and those with normal keratometry.

Thus, we can say that the Barrett's formula can be used with predictable outcomes in children under 2 years of age and above 5 years, in eyes with axial length between 21 mm and 24 mm and in those with flat corneas.

Few limitations of our study include its retrospective nature and smaller sample size in some of the subgroups. Further studies with larger sample size are needed to validate the results and achieve a statistically significant conclusion.

CONCLUSION

Though there is no ideal formula for IOL power calculation in children, our study concludes that Barrett's formula can be used with predictable outcomes in children under 2 years of age and above 5 years, in eyes with axial length between 21 mm and 24 mm and in those with flat corneas.

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TABLES

Table 1: The number of eyes in different subgroups

Criteria	Subgroups	Number of eyes
Axial length (in mm)	18-21	16
	22-24	50
	>24	6
Keratometry (in dioptres)	</= 45	44
	>45	28
Age (in years)	</= 2	23
	3-5	30
	6-8	19

Table 2- Comparison of the prediction error(PE) and absolute prediction error(APE) using SRK-II and Barrett's formulae in the axial length group

Axial length	PE(SRK-II)	APE (SRK-II)	PE (Barrett's)	APE (Barrett's)
18-21 mm n=16	-0.06±0.95	0.75±0.56	1.37±1.45	1.5±1.31
21-24 mm n=50	-0.63±1.05	0.94±0.78	-0.11±1.05	0.70±0.78
>24 mm n=6	-1.83±1.18	1.83±1.18	-1.62±1.35	1.62±1.35
p-value	0.007	0.119	0	0.008

Table 3: Comparison of the prediction error(PE) and absolute prediction error(APE) using SRK-II and Barrett's formulae in the keratometry group

Groups	PE(SRK-II)	APE(SRK-II)	PE(Barrett's)	APE(Barrett's)
≤ 45 Diopters n=44	-0.90±1.04	1.04±0.91	0.04±1.15	0.79±0.83
>45 Diopters n=28	-0.13±1.07	0.85±0.63	0.16±1.75	1.2±1.26
p-value	0.013	0.698	0.722	0.102

Table 4: Comparison of the prediction error (PE) and absolute prediction error(APE) using SRK-II and Barrett's formulae in the age group

Groups	PE(SRK-II)	APE(SRK-II)	PE(Barrett's)	APE(Barrett's)
≤ 2 years n=23	-0.15±0.84	0.67±0.50	-0.07±1.71	1.20±1.19
3 - 5 years n=30	-0.99±1.29	1.32±0.94	0.1±1.51	1±1.11
5 - 8 years n=19	-0.54±0.9	0.76±0.71	0.09±0.74	0.56±0.47
p-value	0.02	0.017	0.311	0.104

Table 5: Correlation between axial length and prediction error for SRK-II and Barrett's formulae

Groups	PE(SRK-II)	APE(SRK-II)	PE(Barrett's)	APE(Barrett's)
Overall AXL (mm) n=72	-0.5 (0)	0.39(0)	-0.72(0)	-0.16(0.17)
18-21 mm n=16	-0.54(0.02)	-0.01(0.95)	-0.77(0)	-0.18(0.49)
21-24 mm n=50	-0.27(0.05)	0.26(0.06)	-0.46(0)	-0.07(0.6)
>24 mm n=6	-0.93(0)	0.93(0)	-0.82(0)	0.82(0.04)

Table 6: Correlation between keratometry and prediction error for SRK-II and Barrett's formulae

Groups	PE(SRK-II)	APE(SRK-II)	PE(Barrett's)	APE(Barrett's)
Overall K (Diopters) n=72	0.3(0.01)	-0.1(0.37)	-0.72(0)	-0.16(0.17)
K<45 D n=44	0.04(0.76)	0.01 (0.94)	-0.24 (0.11)	-0.04 (0.75)
K> 45D n=28	0.07 (0.7)	-0.12 (0.52)	0.36 (0.05)	0.07 (0.69)

Table 7: Correlation between age group and prediction error for SRK-II and Barrett's formulae

Groups	PE (SRKII)	APE (SRK II)	PE (Barrett's)	APE (Barrett's)
Overall age (years)	-0.09 (0.46)	0.01 (0.93)	-0.03 (0.83)	-0.24 (0.048)
≤ 2 years n=23	-0.02 (0.25)	0.09 (0.66)	-0.27 (0.2)	-0.07(0.75)
3-5 years n=30	0.15 (0.41)	-0.04 (0.81)	-0.07 (0.69)	0.06 (0.72)
5-8 years n= 19	0.31 (0.18)	-0.25 (0.29)	0.15 (0.53)	0.29 (0.22)

This paper was judged as the BEST PAPER of Pediatric – II Session

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POSTERIOR PHAKIC INTRAOCULAR LENS FOR TREATMENT OF REFRACTIVE AMBLYOPIA IN CHILDREN AND ADOLESCENT

ABSTRACT

Purpose – To analyze the demographics and clinical outcomes of posterior chamber phakic intraocular (IOL) implantation for refractive amblyopia in children and adolescents.

METHODS

A prospective interventional study was performed on children and adolescents with amblyopia at a tertiary eye care center from January 2021 to March 2023. Twenty-three eyes of 21 anisomyopic and isomyopic amblyopia patients who underwent posterior chamber phakic IOL (Eyecryl phakic IOL) surgery as a treatment for amblyopia were included in the study. Patient demographics, pre and post-operative visual acuity, cycloplegic refraction, anterior and posterior segment examination, intraocular pressure, pachymetry, contrast sensitivity, endothelial count, patient satisfaction scores and stereopsis were evaluated. Patients were followed up at day one , six weeks, three months and 2 year after surgery, and visual outcomes and complications were documented.

RESULTS

The mean age of patients was 14.16 ± 3.49 years (range 10-19). The mean intraocular lens power was -12.20 diopter spherical (DS) in 23 eyes and -2.25 diopter cylindrical (DC) in 4 patients. The mean unaided distant visual acuity (UDVA) and best-corrected visual acuity (BCVA) were 1.39 ± 0.25 and 0.40 ± 0.21 preoperatively on the log MAR chart. Postoperatively the visual acuity improved by 2.6 lines in 3 months period and maintained till two years. Post-surgery, contrast sensitivity in the amblyopic eyes significantly improved, and the average endothelial loss recorded was 5.78 % at one year which was statistically insignificant. Patient satisfaction score was statistically significant, with 4.736/5 recorded on the Likert scale.

There was a very slow improvement in stereopsis from 75 second of arc to 61 second of arc at 2 years.

CONCLUSION:

Posterior chamber Phakic IOL is a safe, effective, and alternative method for treating amblyopia patients who are non-compliant with glasses, contact lenses, and kerato-refractive procedures.

Keywords – Anisomyopic, Isomyopic, Amblyopia, Phakic IOL, Anisometropia

TRANSLATIONAL RELEVANCE:

This study will pave way for a new and acceptable method for managing Anisomyopic and Isomyopic Amblyopia in young and adolescent patients. This is the first such registered clinical trial from India reporting the application of phakic IOL as an alternative and effective treatment in amblyopia associated with anisomyopic and isomyopic patients.

INTRODUCTION

Amblyopia is a neurodevelopmental ocular disease manifested as monocular and binocular impairments, including vision reduction, contrast sensitivity, or even loss of stereoscopic vision[1]. Amblyopia is classified as– refractive, strabismus, and visual deprivation subtypes. The reported prevalence of amblyopia globally is 1-5%. Further, there are three types of refractive amblyopia– isometropia, anisometropic and meridional. The most common type of amblyopia is anisometropic, followed by strabismus and mixed strabismus and anisometropic types. Refractive correction with spectacles and contact lenses and occlusion therapy are the traditional treatments for refractive amblyopia. However, these modes of treatment are associated with poorer compliance as children find it difficult to wear glasses and contact lenses because of foreign body sensations and chances of corneal infections[2]. Also, there are many psychosocial issues faced by children, like bullying and harassment associated with glass use, especially if these are thicker and associated with higher refractive errors. Therefore, there is a strong need for alternative treatment strategies to manage pediatric and adolescent patients with high myopic amblyopia. Photorefractive keratectomy (PRK), laser keratomileusis (LASIK), and laser-assisted subepithelial keratectomy (LASEK) have emerged as alternate corneal refractive surgery techniques that are effective as well as safe in children and young adults who were not compliant to conventional approaches[3-8]. For pediatric and young adults with refractive amblyopia who could not undergo refractive laser surgery techniques, phakic intraocular lens (IOL) implantation is an effective surgical correction technique in managing amblyopia[9-13].Althomali reported toric phakic IOL implantation in 6 eyes of 6 amblyopic patients aged 5 to 15 years and proved that it is a viable therapeutic modality for treating children with anisometropic amblyopia. Zhang et al. observed no complications with posterior chamber implantable

Collamer lens in adults with high myopia with anisometropic amblyopia. They also observed improved visual acuity, contrast sensitivity, and binocular vision. However, there is limited literature on phakic IOL implantation in pediatric and adolescent patients in the Indian scenario. Keeping this in mind, through this study, we aimed to analyze the effectiveness and safety of posterior chamber phakic intraocular lens (Eyecryl) implantation for the treatment of pediatric and adolescent Indian patients with unilateral and bilateral refractive amblyopia secondary to high myopia.

METHODS

This was a prospective study performed on 23 eyes of 21 refractive amblyopia patients due to myopia or myopic astigmatism from January 2021 to March 2023 at a tertiary care center. The study was conducted in accordance with the Declaration of Helsinki after obtaining approval from the Institutional Ethics Committee. Written informed consent was obtained from all the patients or parents/guardians in the case of minors. It is the first such registered clinical trial regarding Phakic IOL as a treatment modality in amblyopes in India. The Clinical Trial Registry of India number is CTRI/2021/01/030394. The inclusion criteria were as follows: patients aged 10-19 years; corrected distance visual acuity (CVDA) recorded on the log MAR chart in the amblyopic eye < 0.2; poor compliance with glasses or contact lenses, and occlusion therapy; anterior chamber depth of > 2.8 mm; endothelial density more than 2700 cell/mm2; amblyopia due to myopia or myopic astigmatism. The exclusion criteria were patients with hypermetropic amblyopia; strabismic amblyopia; any history of glaucoma, active inflammation, cataract, previous intraocular surgery, or any other ocular disease.

A complete preoperative detailed ophthalmic evaluation was performed on all the patients. The detailed evaluation included noting the demographics, unaided distant visual acuity (UDVA), and best-corrected visual acuity (BCVA) by Early Treatment of Diabetic Retinopathy Study (ETDRS) chart, cycloplegic refraction, slit lamp anterior and posterior segment examination, Hirschberg corneal reflex for ocular alignment, cover, uncover and alternate cover test, applanation tonometry for measuring intraocular pressure (IOP), contrast sensitivity, corneal topography, pachymetry, and specular microscopy. Optical coherence tomography (OCT) was performed in selected patients as and when indicated.All patients were given a trial of patching for a minimum of 6 months before embarking onto the surgery. All patients underwent Phakic IOL implantation. The intraocular lens size for implantation was measured with the help of calipers as– horizontal white-to-white (WTW) distance with an addition of 1.5 mm to that value. In patients requiring cylindrical correction, the axis was marked under a slit lamp in a sitting position pre-operatively.

PHAKIC INTRAOCULAR LENS AND SURGICAL PROCEDURE.

The same surgeon (AKM) operated on all cases under topical anesthesia with proparacaine 0.5% or under general anesthesia. 1% Cyclopentolate and 2.5% phenylephrine eye drops were applied to achieve pharmacological dilatation 60 minutes prior to surgery. A 2.8 mm temporal clear corneal incision was placed, and viscoelastic material was injected into the anterior chamber. Two side ports were fashioned, each being two clock hours away from the main incision, with a 15-degree blade for positioning the IOL. Eyecryl phakic IOL was injected through the main incision behind the iris, and all four haptics were positioned in the sulcus. After positioning the IOL

with a sinskey hook, intracameral 1% pilocarpine was instilled for constricting the pupil. Then viscoelastic material was aspirated, and the anterior chamber was washed thoroughly and formed with a basal salt solution. Topical 0.5% Moxifloxacin and 0.1% dexamethasone, and Carboxymethylcellulose 0.5% were prescribed four times per day for six weeks in tapering doses in the postoperative period. On follow-up, UDVA and BCVA, anterior segment and posterior segment details, IOP, endothelial cell count, pachymetry, and contrast sensitivity were recorded on day 1,6 weeks, 3 months and 2 year . Postoperatively, occlusion therapy was prescribed for the dominant eye for three months. The duration of occlusion therapy per day was based on the guidelines laid by the pediatric eye disease investigator group. **(Figure 1 & 2)** We also assessed the patient satisfaction score using the Likert scale scoring at 12 weeks follow-up visit.

STATISTICAL ANALYSIS

Data were entered into an excel sheet and transferred to SPSS version 21 for analysis. Mean, and standard deviation was calculated for all the parametric data. Paired t-test was used for before and after mean difference calculation, and the Kruskal-Wallis test was used for skewed visual acuity data. The patient satisfaction score was assessed using the Likert scale.

RESULTS

Demographics- Age and Visual acuity

Twenty-three eyes of 21 patients were included in the study. The mean age (SD) of the patients was 14.16 (±3.49) years (range: 10-19). The mean preoperative Log MAR UDVA and CDVA were 1.39 ± 0.25 (range: -1.10 to 1.80) and 0.40±0.21 (range: -0.20 to 0.80), respectively. All patients completed were followed up on day 1 , 6 weeks , 3 months and 2 year after surgery (**Table 1-3)**. The mean post-operative Log Mar UDVA of the

amblyopic eye at one day, six weeks, three months and 2 year was 0.27± 0.18, 0.21±0.19,0.16±0.18 and 0.17±0.16 respectively. Similarly, the mean post-operative Log Mar CDVA of the amblyopic eye at one day, six weeks, three months and two year was 0.20±0.11, 0.13±0.12, 0.11±0.13 and 0.11±0.12 respectively. None of the patients lost any lines of visual acuity after surgery.

CONTRAST SENSITIVITY

Preoperatively recorded contrast sensitivity was 1.0750 +/- 0.2118, and it improved to 1.6500+/-0.21669 at three months postoperative period and was same up to 2 year . Contrast sensitivity significantly increased in the post-operative period and was significant. The average gain in the post-operative contrast sensitivity was 0.59 (SD: ±0.196), compared to pre-op contrast sensitivitywith a p-value of<0.001 **(Table 4)**

INTRAOCULAR PRESSURE

The IOP for the amblyopic eye changed from 15.2+/-2.52 mmHg preoperatively to 17.29+/-5.0 mm Hg at 3 months to 15.29+/-0.34 at 2 year post-surgery, and the difference was not statistically significant as recorded till a year. **(Table 5)**

ENDOTHELIAL CELL COUNT

The mean endothelial cell count (ECD) was 3131.33 +/-181.01 (range: 2832 to 3431) cells/mm2 preoperatively and 2981 +/-171.62 (range: 2745 to 3265) cells/mm^2 at the last follow-up time postoperatively, without any significant endothelial cell loss. The mean difference between pre-op endothelial cell density and post-op endothelial cell density was149.70, SD: ±35.033. The average endothelial cell loss was 5.78% at 2 year .**(Table 6)**

PATIENT SATISFACTION SCORE

The patient satisfaction score was assessed by the Likert scale (range 0-5). Seventeen patients gave a score of five, and six patients gave a score of four. The mean patient satisfaction scores were 4.736 +/- 0.36 (range 1-5). **(Table7)**

Intraocular Lens (IOL) power

All patients underwent the sulcus implantation of IOL with mean phakic IOL power of – 12.20 Dioptre spherical, with four patients having added toricity of -2.25 Dioptre Cylindrical . **(Table 8)**

Stereopsis

There was a very slow improvement in stereopsis from 75 second of arc that was same on post-op day 1 and improved to 71 and 67 on second and third follow-up respectively with no significant p-value. At 1year it improved to 61 second of arc that remains stable at 2 years.**(Table 9) It was most rigid in terms of improvement.**

COMPLICATIONS

Only two eyes had raised IOP at one day and six weeks , 38 mm Hg and 40mm Hg postoperatively, and were successfully treated by short-term anti-glaucoma medications topical timolol - brimonidine eye drops two times and discontinuing of steroid eye drops, and no other intraoperative or post-operative complications noted. No general anaesthesia complications were observed. No other complications like cataract , retinal – detachment ,IOL dislocation, pupillary block glaucoma and pigmentary deposits were observed in a long follow up period of two year. Not a single eye underwent phakic IOL explantation .

DISCUSSION

Contact lenses and glasses are conventional methods of treatment of amblyopia, but the patients are not compliant with the above methods. Laser

refractive method such as LASIK or PRK has been preferred alternative methods as they improve refractive -amblyopia permanently. Complications such as corneal haze in PRK[7-8], and flap related complications in LASIK were reported along with keraectasia and corneal-thinning[6], so posterior chamber phakic intraocular lens are the preferred procedure of treatment of refractive amblyopia[14-16] because of its advantages such as better contrast sensitivity, less high order aberration[17-18]and no flap related complications as reported in LASIK and no incidence of corneal – ectasia and thinning. Anterior chamber phakic IOL and posterior phakic IOL were approved by US Food and Drugs Administration to treat refractive amblyopia in adults[9]. Only a few cases - reports are available regarding the use of phakic IOL in treating amblyopia in children and young adults in the research literature[10].

Lesueur and Arne[9] reported five eyes of 4 children in the age group of 3 to 16 years who underwent phakic IOL for anisometropic amblyopia. No complications were noted within 11.80 month follow-up period and visual acuity improved by three or more Snellen's lines. Benz Ezra[11] conducted a study on three female patients (age 9 to 18 years) with anisometropic amblyopia, result showed that BCVA improved in all patients and stereopsis in 2 patients at nine months of follow up. Temporary pigmentary dispersion was reported in one case. Althomali[12] said six children with anisometropic amblyopic underwent toric phakic IOL, and three lines of visual acuity improvement were noted in 6 eyes. All phakic IOLs were well centered on 24 months follow-up.

The disadvantages of corneal haze and flap-related complications in corneal refractive procedures have led to a search for a newer treatment modality for refractive amblyopia in children and young adults.

In our study, 23 anisomyopic and isomyopic amblyopic eyes were operated on with phakic PCIOL (Posterior chamber intraocular lens) implantation to correct refractive amblyopia in children and young adult. Post-operative contrast sensitivity improved significantly compared to the preoperative period at one year of follow-up. The visual acuity continued to improve considerably from 1 day to 3 months after phakic PCIOL implantation and maintained till 1 year without anyone losing one line of the log MAR chart, which was consistent with the study conducted by Lesueur and Arne, where the preoperative spherical equivalent of -12.8D, showed a post-operative gain of 3 or more Snellen's line. The study by Ben Ezra et al., Where anisometropic amblyopia and myopia of -6D to -16D were operated, showed significant improvement in visual acuity and binocular function in the 9 months follow up period[11]. Study by Alio et al., with a follow-up period of 5 years, shows improvement in visual acuity of one log MAR line and no complications. Contrast sensitivities of amblyopic eyes in the low and mild spatial frequencies (0.5, 1, 2 cycles per degree) post-operative were better than preoperative and significantly increased with follow-up time postoperatively. However, there was no improvement in stereopsis at one year follow-ups in our study.

Assil reported an endothelial loss of 6.5% to 15.2% over three years of follow up on patients who underwent Iris fixated phakic IOL for anisometropic amblyopia[19]. Ali et al. in their retrospective study of 10 children who underwent PIOL implantation (9 eyes with iris-fixated Phakic IOL and one eye with aphakic PCIOL), showed that BCVA improved in all children[20]. Five years after surgery, endothelial cell count was >2000 cells/mm^2 in eight (80%) patients. There was no significant endothelial cell loss in our study at twelve months after surgery (5.78%). However, regular long-term follow-ups will elucidate more intricate results.

In earlier studies, post-operative complications such as cataract, dislocation of phakic IOL, pupillary block glaucoma, and retinal detachment have been described[21]. Implantable Collamer Lens implantation and Food and Drug Administration studies have stated that cataract was a significant complication with an incidence of 2.1 % within one year and 2.7% within three years of post-operative follow up[22].

Only 2 cases of raised IOP were reported and dropped generally after treatment with anti-glaucoma medication, and discontinuing steroid eye drops as raised IOP may be attributed to the use of steroids postoperatively. No other complications such as cataract, retinal detachment, IOL dislocation, pupillary block glaucoma, and pigmentary deposits were reported in our study. Not a single case of pupillary block glaucoma may be attributed to the unique design of this phakic IOL with three holes – one in the centre and two in the peripheral haptics for uninterrupted passage of aqueous .

Our study results revealed that phakic PCIOL is the preferred method of correction of refractive amblyopia in children and young adolescents who are intolerable to contact lenses and unsuitable or unwilling to go for LASIK-like procedures. The phakic intraocular lenses provide the advantages such as reversibility and ability to exchange IOL, predictability, high visual quality, preservation of accommodation, lack of regression, and retinal magnification in myopic eyes. However, complications such as Endothelial cell loss, dislocation, pigment dispersion, and shallow anterior chamber can be encountered. More follow-ups are needed to assess the complication and safety in the long–term period.

VALUE STATEMENT

What Was Known

The treatment of amblyopia include cumbersome occlusion therapy, penalization method which hampering day to day activities, thick contact lenses, and irreversible LASIK procedure

WHAT THIS PAPER ADDS

This is the first successful, registered clinical trial to assess the use of Phakic intraocular lens as treatment modalities of amblyopia in children & adolescents with a follow up period of 1 year. It is a simple, easy, reversible procedure for the treatment of amblyopia to improve visual acuity, increase contrast sensitivity, least endothelial damage, and high-grade patient satisfaction.

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FIGURE LEGENDS

Figure 1– Eyecryl Phakic Toric IOL

Figure 2 – Post operative image of the eye phakic Eyecryl Phakic toric IOL

Table 1: Age distribution of the study participants (N=23)

S. No	Age	Frequency	Percentage
1	10	3	13.04
2	11	4	17.39
3	12	3	13.04
4	13	1	4.34
5	14	4	17.39
6	15	2	8.69
7	17	6	26.08
8	Total	23	100
	Mean + SD	14.16+/- 3.49	

Table 2: Sex distribution of the study participants (N=23)

S. No	Sex	Frequency	Percentage
1	Male	12	52.17
2	Female	11	47.83
3	Total	23	100

Table 3a. Depicting the mean and standard deviation of Pre Operative vision uncorrected to 3rd visit

S. No	Parameter	Mean	Standard deviation
1	Pre-operativeUDVA	1.39	0.25
2	Post-operative day 1 UDVA	0.27	0.18
3	Post-operative1 week UDVA	0.21	0.19
4	Post-operative 3 month UDVA	0.16	0.18
5	Post-operative 1 Year UDVA	0.17	0.16
6	Pre-operative BDVA	0.40	0.21
7	Post-operative day 1 BCVA	0.20	0.11
8	Post-operative 1 week BCVA	0.13	0.12
9	Post-operative 3 month BCVA	0.11	0.13
10	Post-operative 1 Year BCVA	0.11	0.12

Table 3 b.Depicting uncorrected vision change from pre operative to 3rd visit after operation

S. No	PatientVisit	Mean difference	Standard Deviation	Standard Error Mean	95% Confidence Interval of the Difference		P-value
					Lower	Upper	
1	Pre operative Vision	1.11667	0.24613	-	-		-
2	Post operative Vision uncorrected Day 1	-	-	0.05024	1.01274	1.22060	.000
3	Post operative Vision uncorrected 1st visit	0.05619	0.08990	0.01800	0.01900	0.09957	0.005
4	Post operative Visionuncorrected 2nd visit -	0.05417	0.08330	0.01700	0.01899	0.08934	0.004
5	Post operative Visionuncorrected 3rd visit -	0.05399	0.08110	0.01600	0.01869	0.08754	0.003

Table 3c. Depicting post operative average gain of visual acuity

S. No	Postoperative day	Uncorrected Visual acuity gain	Best corrected visual acuity gain
1	Day 1	11.3	1.3
2	First Visit	11.7	2.6
3	Second visit	12.1	2.6
4	Third Visit	12.1	2.6

Table 4: Comparison of Contrast sensitivity between pre-operative and post-operativeperiod

S. No	Patient Visit	Constrast Sensitivity Mean	Mean difference with Pre op	P Value
1	Pre-OP	1.07	-	-
2	Post OP 1st day	1.26	0.19	0.01
3	Post OP 1stvisit	1.65	0.58	0.01
4	Post OP 2ndvisit	1.66	0.59	0.01
5	Post OP 3rdvisit	1.66	0.59	0.01

Table5: Comparison of IOP between pre-operative and post-operative period

S. No	Patient Visit	IOP Mean	Mean difference with Pre op	P Value
1	Pre OP	15.25		-
2	Post OP 1st day	16.41	1.16	0.99
3	Post OP 1stvisit	16.83	1.58	0.01
4	Post OP 2ndvisit	17.29	2.04	0.18
5	Post OP 3rdvisit	15.29	0.34	0.11

Table 6: Depicting pre-operative and post-operative endothelial cell count

S. No	Patient Visit	Mean	N	Standard Deviation	Standard Error Mean
1	Pre-operative endothelial cell count	3131.33	23	181.099	36.967
2	Post-operative endothelial cell count at 1 Year	2981.63	23	171.627	35.033

Table -7 Table depicting patient satisfaction rate (N=23)

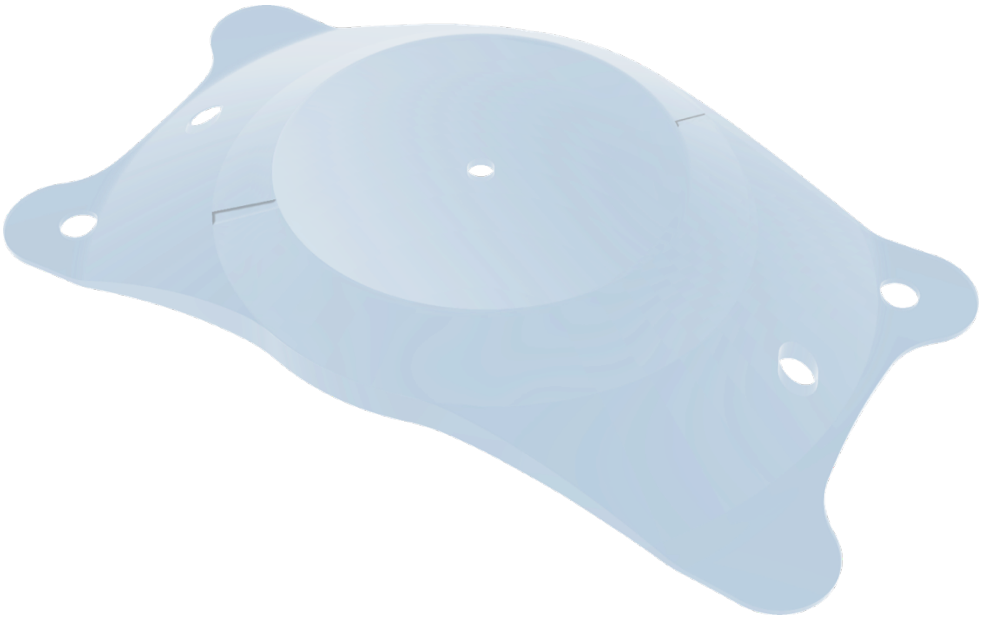
S. No	Patient Satisfaction Score	Percentage (%)
1	1	0%
2	2	0%
3	3	0%
4	4	26%
5	5	74%

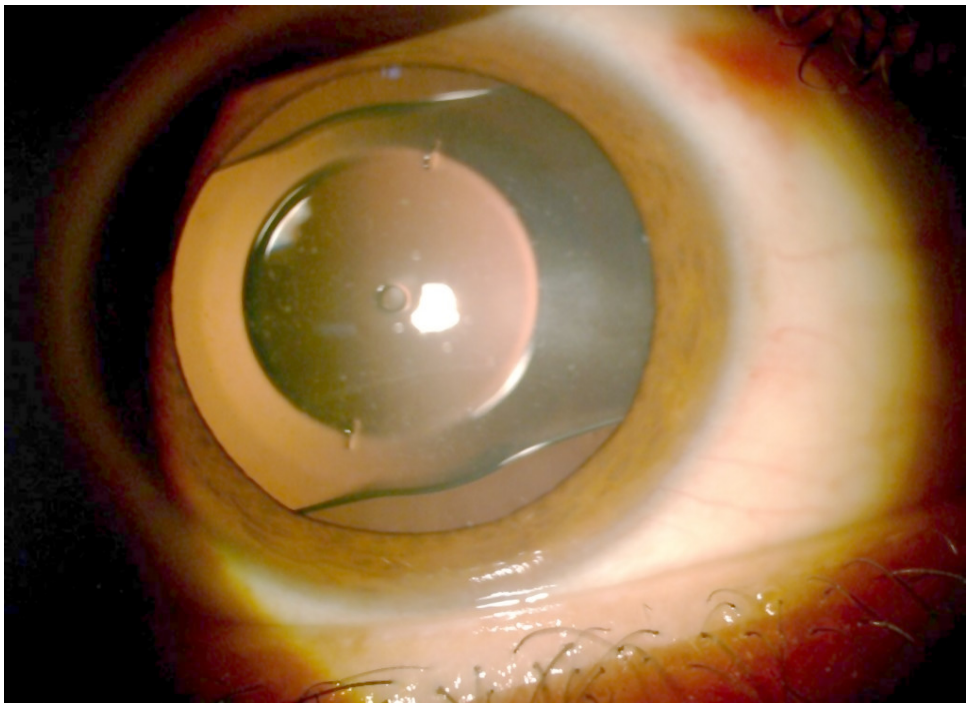
Table 8: Descriptive statistics of IOL (N=23)

S. No	Variable	Mean	SD	Toricity (n=4)
1	IOL	-12.20 DS	1.531	-2.25 DC

Table 9. Changes in Stereopsis during follow –up period

S. No	Patient Visit	Stereoacuity	Mean difference with Pre op	P Value
1	Pre OP	75.25+/- 40.29		-
2	Post OP 1st day	75.25+/- 40.29	NA	NA
3	Post OP 1stvisit	71.38+/-39.45	3.87	0.18
4	Post OP 2ndvisit	67.29+/-39.05	7.96	0.11
5	Post OP 3rdvisit	61.23+/-30.98	14.02	0.01





This paper was judged as the BEST PAPER of Refractive Surgery Session

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DOUBLE ANTERIOR, SINGLE POSTERIOR (DASP) DELINEATION TECHNIQUE FOR CORRECT PLANE DISSECTION IN SMILE

ABSTRACT

Purpose: To describe a new technique for performing lenticule dissection in small-incision lenticule extraction (SMILE) surgery along with the use of a novel 'release sign' to avoid lenticule misdissection.

Methods/Surgical Technique: After femtosecond laser application for SMILE surgery, the anterior and posterior planes were delineated. With our technique, posterior plane delineation is performed in the central 1 mm area with anterior plane delineation being performed on both sides of the cap side cut. The 'stop sign' is elicited at both the edges of posterior plane delineation, which we call the 'double stop sign'. During dissection of the anterior plane, a novel 'release sign' is noted with a sudden release of resistance when the dissection moved from one area of the anteriorly delineated plane across the undissected region to reach the second area of the already delineated anterior plane of lenticule. This provides reconfirmation that the dissection remains in the correct plane and avoids unintentional initial posterior plane dissection.

Conclusion: Double anterior, single posterior (DASP) delineation technique along with implementation of the 'release sign' is a valuable tool for surgeons beginning their journey with SMILE. It significantly reduces the risk of complications related to lenticule misdissection and shortens the surgeon's learning curve.

Keywords: SMILE surgery, DASP technique, Release sign, Lenticule dissection

INTRODUCTION:

Keratorefractive procedures have significantly evolved to now provide multiple options of laser vision correction for varied refractive errors. Small-incision lenticule extraction (SMILE) surgery marks a paradigm shift from flap-based laser-assisted in-situ keratomileusis (LASIK) and femtosecond-LASIK procedures, to flapless creation of an intrastromal lenticule using the femtosecond laser, that is extracted through a small (2-5 mm) incision.[1] SMILE is safe, effective, and predictable for the correction of myopia and myopic astigmatism.[2,3]

Along with avoiding all flap-related complications associated with LASIK, presents advantages of leaving an intact anterior stroma with better biomechanical strength, reduced incidence of dry eyes, and faster corneal re-innervation.[4,5] However, the technique remains surgically challenging with a steep learning curve. A high incidence of intraoperative complications may be observed during the initial learning phase, and the majority of these are a result of difficult lenticule dissection and extraction.[6] The correct identification and dissection of varying lenticule planes can be particularly challenging for novice surgeons. We describe a novel technique - the double anterior, single posterior (DASP) delineation technique for correct lenticule plane identification and dissection. Along with this technique, we describe a

new 'release sign' which acts as a reconfirmation of dissection remaining in the designated plane.

SURGICAL TECHNIQUE:

According to the patient's refractive error and the surgeon's preference, parameters are set on the VisuMax femtosecond laser (Carl Zeiss Meditec, Jena, Germany). After ensuring adequate centration, suction is activated and the femtosecond laser is fired. During SMILE, the femtosecond laser creates four sequential cuts to fashion an intrastromal lenticule. The lower interface of the lenticule is cut first, in a spiral-in pattern, followed by a 360-degree side cut. This is followed by the creation of the upper interface of the lenticule (also the under-surface of the cap) in a spiral-out pattern with a final 2-5 mm access incision (cap side-cut).[7] This is followed by the freeing of the lenticule from surrounding stroma, with the anterior plane dissection being performed first, followed by the posterior plane dissection.

For our DASP delineation technique, we preferred a superior 3 mm incision. A sharp-tipped instrument is used to open the cap side cut incision. For delineation of the anterior plane, the dissector is first taken sideways towards the periphery, in the gap between the lenticule edge and cap edge, and then turned inwards toward the lenticule edge to enter the anterior plane. As the anterior plane and undersurface of the cap are in continuation with each other, the dissector is more likely to enter the anterior plane in this manner. Anterior delineation is performed in a 1 mm area on the left end of the cap side-cut first. This is followed by a second area of anterior delineation using a similar entry technique at 1 mm on the right end of the cap side-cut (figures 1 and 3). Following delineation of the two anterior plane edge regions, the dissector is entered straight in from the central 1 mm of cap side-cut with slight posterior pressure on the cornea. This ensures entry into the

posterior plane. Delineation of the posterior plane is performed by overlapping the dissector with previously dissected anterior planes on both the right and left sides. The stop sign, as described previously by Sachdev et al,[8] is thus demonstrated at both edges during posterior plane delineation, resulting in a 'double stop sign' (figures 2 and 3). If the instrument is correctly placed in the posterior plane centrally and the initial dissection has been accurately performed in the anterior plane at both ends, a point of resistance is noted at the junction of dissected and undissected areas of both planes, and at both ends. This gives dual confirmation of initial dissection being solely in the anterior plane and central dissection occurring in the posterior plane. However, if one of the initially delineated areas is not anterior to the lenticule but is in the posterior plane, and resistance is only evidenced at one end during posterior plane delineation, there will be a sudden release of the instrument when it reaches the already wrongfully dissected part of the posterior plane (the release sign). If the 'release sign' is present during posterior plane delineation, then anterior dissection of the lenticule should begin from the other end, where the 'stop sign' has been elicited (see supplemental video).

Next, the longer blunt dissector is used to enter through one of the anteriorly delineated areas and dissection is proceeded in the usual fashion. The 'release sign' is again demonstrated while performing complete anterior plane dissection. If both areas of the anterior plane delineation have been initially identified correctly, when dissection is started from one of the anterior delineated areas, as soon as the long dissector reaches the already delineated opposite anterior region, there is an evidence of sudden release of resistance. Thus, this release of resistance results in ease of movement for the long dissector to reach the lenticule edge, specifically termed the 'release sign' (see supplemental video). This gives a reconfirmation of correct

anterior plane dissection. Entry for posterior plane is performed from the central region and complete dissection is successfully performed with the long dissector. There is no 'release sign' noted during posterior plane dissection. The lenticule is then extracted with a microforceps. Interface is washed thoroughly with saline and surface dried with a surgical sponge to complete the procedure.

DISCUSSION:

SMILE procedure has become increasingly popular amongst refractive surgeons across the world but remains challenging surgically with a steep learning curve.[6] During SMILE, It is recommended to dissect the anterior plane of the lenticule before proceeding with posterior plane dissection to avoid cap-lenticular adhesion.[6,7] Novice surgeons may find it difficult to correctly identify anterior and posterior planes resulting in unintended initial posterior plane dissection. This may cause cap-lenticular adhesion, resulting in increased surgical time, poorer tissue handling, delayed visual recovery, and suboptimal visual outcomes.[9] Various techniques and signs have been described to correctly identify the plane of dissection. These include the previously reported white ring sign, shimmer sign, meniscus sign, and stop sign which are all noted at different steps to avoid lenticule misdissection.[8-11] Also, conventionally, initial anterior and posterior plane delineation is performed in right and left regions of the cap side-cut.[6,8] If what is thought as the area of anterior delineation has unintentionally resulted in posterior plane delineation, misdissection of the lenticule with cap-lenticular adhesion may occur.

We describe a simple technique of SMILE lenticule dissection that gives multiple confirmations to the surgeon that the dissection is in the right plane. The double anterior single posterior delineation technique involves entry to

be initiated in a curved sideways manner, first into the region between lenticule edge and cap edge, beyond the side cap cut. The dissector is then directed into the anterior plane of lenticule which is in continuation with the cap cut. This manoeuvre likely impedes entry into the posterior plane, as the posterior lenticule surface is not in continuation with the undersurface of the cap and lies at a different level. The second step involves delineation of the anterior plane on both right and left sides with posterior plane delineation occurring centrally. The 'double stop sign' can then be noticed at both edges of posterior plane delineation.

The third step involves anterior plane dissection where we describe the 'release sign'. As you enter from one side into the anterior plane and reach the already dissected region on the other side of the anterior plane, a sudden release of resistance is noted. Therefore, with the use of these multiple checkpoints in the DASP delineation technique during SMILE surgery, the surgeon can be confident to correctly perform the lenticule dissection and avoid major complications. Moreover, if there has been an inadvertent initial posterior plane dissection, this technique ensures an area of entry for anterior plane dissection as the surgeon has made two entries into the anterior plane during initial delineation. Therefore, even if one of the areas of anterior delineation is in the correct plane, it can easily result in rescuing the surgeon from cap lenticular adhesion, where anterior plane identification becomes challenging. While it may be argued that a novice surgeon may perform the delineation in a reverse manner with edges having inadvertent posterior plane delineation and central region having inadvertent anterior plane delineation. This would then result in initial unintended posterior plane dissection and cap lenticular adhesion. However, we would disagree with that argument as DASP delineation technique not just involves two areas of anterior plane delineation but the manoeuvring of

instrument for delineation of two planes is entirely different. This differential manoeuvring of instrument for anterior and posterior plane delineation has not been described or published before. It makes posterior plane entry highly improbable on both the sides, even for novice surgeons. Additionally, the 'release sign' described during anterior lenticule dissection reassures the surgeon about correct plane dissection. This 'release sign' during lenticule dissection has also not been described before.

The DASP delineation technique along with the 'release sign' can easily be adapted by novice surgeons, who may experience difficulty identifying previously described signs in their initial cases. The technique also offers similar repeatability and safety for patients with low myopia where the lenticule may be thin and dissection challenging.

The advantages of our technique include simplicity of the procedure, multiple checkpoints during the dissection of lenticule to ensure correct anterior plane dissection first, and an opportunity to complete anterior plane dissection regardless of inadvertent initial posterior plane dissection. The disadvantages of our technique include slightly prolonged surgical time due to two areas of anterior delineation being created and the need for at least 3 mm of cap side-cut incision.

We believe that our DASP delineation technique with the use of 'double stop sign' along with 'release sign' provides an infallible method of correct plane identification and dissection irrespective of the surgeon's experience. It provides a simple, reproducible, dependable, and effective method that can easily be adapted into the armamentarium of every refractive surgeon, significantly shortening their surgical learning curve for SMILE.

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FIGURE LEGENDS:

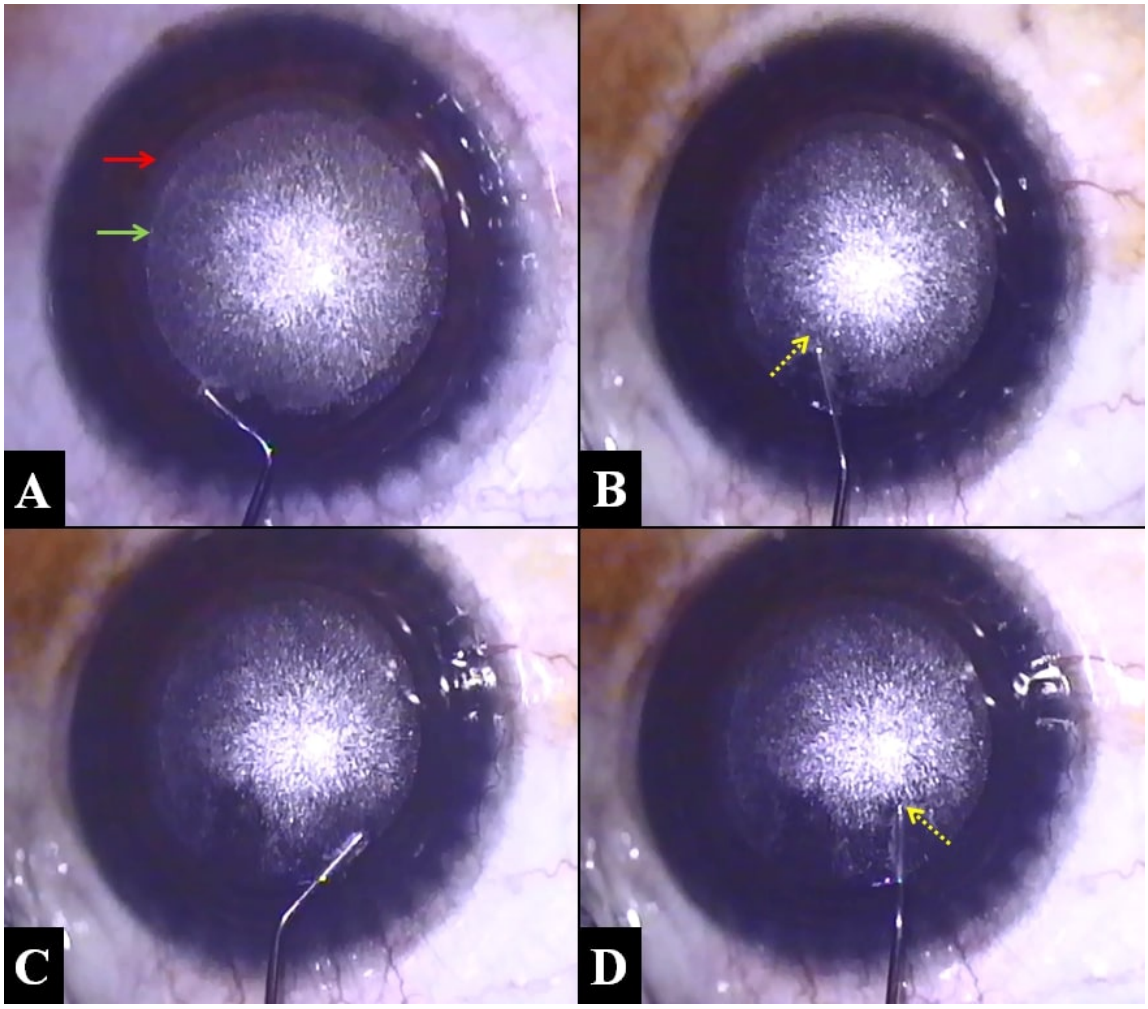
Figure 1. Anterior plane delineation was done on two sides in the DASP delineation technique. A, Red arrow indicates the outer ring corresponding to the cap cut while the green arrow indicates the inner ring corresponding to the lenticule side cut. A and B, Entry of dissector for the left side of anterior plane delineation. Note the direction of entry being in a curved manner, first, in the space between cap edge and lenticule edge, and then curved inwards towards the anterior plane of lenticule (yellow dotted arrow). C and D, Entry of dissector for the second area of anterior plane delineation on right side done in a similar manner. Two areas of anterior plane delineation were identified on both ends of the cap side-cut.

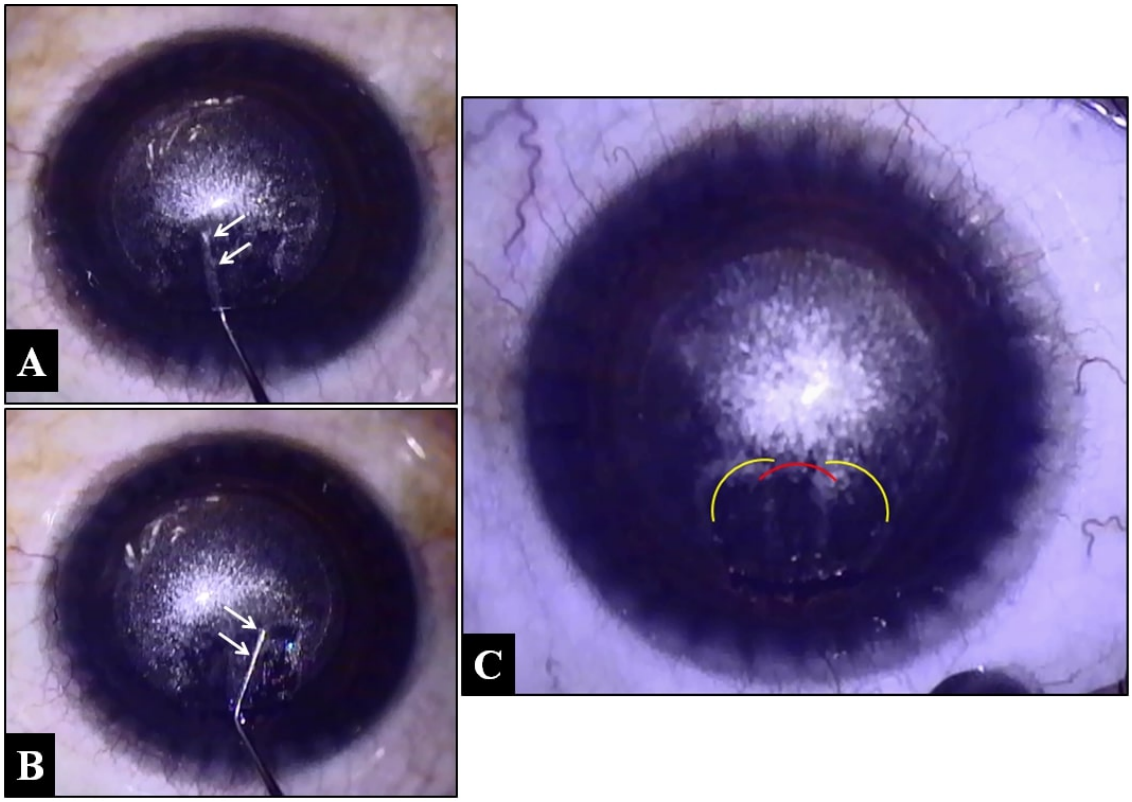
Figure 2. 'Double stop sign' observed during SMILE. A and B, Resistance noted at both junctions of posterior plane delineation where it overlaps with the previously delineated anterior plane. 'Double stop sign' elicited on both edges of posterior plane delineation (white arrows). C, After completion of delineation, the anterior plane of dissection is identified on both sides (yellow arcs) and the posterior plane of dissection is identified centrally (red arc).

Figure 3. Stepwise lenticule dissection using the DASP delineation technique in SMILE surgery. A, Note the way instrument is manoeuvred for anterior plane delineation on both sides of the cap side-cut (red arrows). Entry into

the posterior plane is made straight in with slight posterior pressure on the cornea (green arrow). The area under the yellow arches represents the area of anterior delineation. The central area of posterior plane delineation (red stripes) having partial overlap with anteriorly delineated areas.

B, Green stripes indicate two areas of anterior plane delineation. Red stripes indicate the central single area of posterior plane delineation. Red and green stripes depict the areas of overlap between anterior and posterior delineation lying in different planes. 'Double stop sign' noted at both edges of posterior plane delineation (red arrows) where there is overlap between the two areas of dissection but in different planes (red and green stripes).

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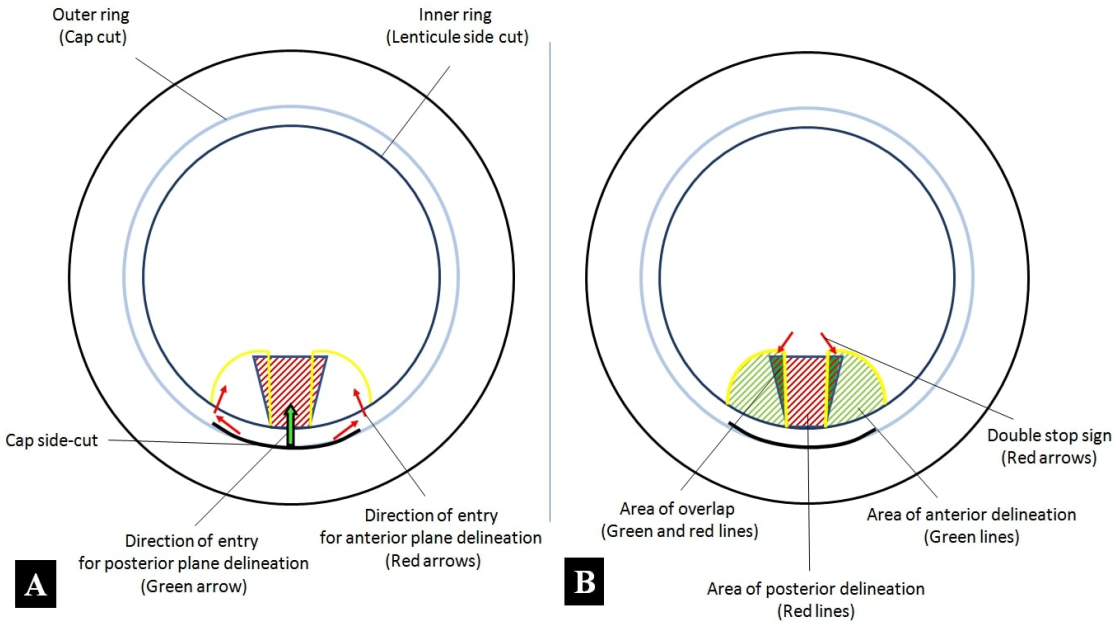
Outer ring
(Cap cut)
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Cap side-cut
Direction of entry
for posterior plane delineation
(Green arrow)
Direction of entry
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(Red arrows)
A
Double stop sign
(Red arrows)
Area of overlap
(Green and red lines)
Area of anterior delineation
(Green lines)
Area of posterior delineation
(Red lines)
B

This paper was judged as the BEST PAPER of Refractive Surgery Session

Dr. RITICA MUKHERJI R22645

Narayana Nethralaya, Bengaluru

ALGORITHMIC APPROACH TO PLAN LASER-BASED CORNEAL COLLAGEN CROSS LINKING IN PROGRESSIVE KERATOCONUS

ABSTRACT:

Objective: Laser-based cross-linking (CXL) has advanced from corneal wavefront-guided (CW) treatment to ocular wavefront-guided (OW) and topo-guided removal of epithelium in keratoconus (TREK). We designed an algorithm to choose the right laser-based CXL in keratoconus (KC).

Methods: Based on corneal curvature, thinnest corneal thickness, corneal and internal aberrations, stromal ablation; patients were divided into CW (35 eyes), OW (123 eyes), TREK (48 eyes) groups. Visual acuity, keratometry, corneal, internal and total ocular aberrations, assessed pre-operatively and post-operatively at 1, 6 months.

Result: BCVA, SEQ, keratometry, defocus, coma, SA reduced significantly ($p<0.05$) in CW and TREK groups. OW group had higher decrease in keratometry, defocus, SA ($p<0.001$). TREK and OW group had lesser tissue ablation ($p<0.001$) vis-a-vis CW group.

Conclusion: This algorithm can be used to customize laser based CXL for ectasia, optimizing tissue ablation and enhancing visual outcomes.

BACKGROUND:

Conventional keratoconus management protocols endeavour to arrest the progression of the disease, and enhance the biomechanical strength of the cornea however fitting contact lenses on such irregular corneas is cumbersome and high irregular astigmatism may not be effectively corrected by spectacles alone. In such cases, laser-based crosslinking offers a better alternative. It maintains the asphericity and results in better spectacle correction and contact lens fitting thereby giving the patient better visual quality.

OBJECTIVES:

1. Identifying patients suitable for laser based crosslinking procedure
2. To assess which patients should be treated by ocular wavefront and corneal wavefront guided treatments based on corneal curvature, thinnest corneal thickness, corneal and internal aberrations and stromal ablation profile.
3. To delineate an algorithm to plan laser-based corrections in ectatic eyes, to select the right candidates for each treatment.

MATERIALS AND METHODS:

It was a prospective interventional study done at a tertiary eye care hospital in South India. The samples were collected following institutional ethics committee approval and informed consent of the study volunteers. Patients with advanced keratoconus with documented progression who were willing for surgery, gave a history of contact lens intolerance and had no evidence of corneal scarring were included. 206 eyes were recruited in the study.

Based on our algorithm which considered corneal curvature, thinnest corneal thickness, corneal and internal aberrations and stromal ablation profile**,** 35 eyes underwent laser-based crosslinking on ORK-CAM module of Schwind-Sirius topographer, 123 eyes underwent OW treatment planned on

Schwind-Peramis topo-aberrometer, and 48 eyes underwent TREK planned on PTK-CAM module of Schwind-Sirius topographer. For patients with TCT > 450 μ, peripheral ablation < 50 μ, central ablation < 30 μ, CW and OW treatments were compared to decide procedure and for those with with TCT < 450 μ, peripheral ablation > 50 μ, central ablation > 30 μ, TREK was planned. Their visual function, tomography and biomechanics were recorded at 1, 3, 6 months post-operatively.

RESULT:

Best corrected visual acuity (BCVA), Spherical equivalent (SEQ), keratometry, CCT, RMS LOA, HOA, defocus, coma 90° and spherical aberration (SA) were reduced significantly ($p<0.05$) in CW & TREK. The OW group had greater fall in keratometry, anterior defocus & SA ($p<0.001$) with lesser tissue ablation ($p<0.001$). TREK and OW group showed fall in RMS of lower ($p=0.15$) & higher order aberrations ($p=0.17$).

DISCUSSION:

Applying this algorithm showed promising results in treatment of keratoconus, can be used to customize treatment of eyes with corneal ectasia, enhancing outcomes & optimizing tissue ablation. Ocular wavefront guided treatment and TREK may be used in corneas not amenable to laser based crosslinking due to higher ablation profiles. Laser based crosslinking can offer a superior visual quality to patients with keratoconus.

This paper was judged as the BEST PAPER of Squint Session

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SURGICAL OUTCOME OF FULL-TENDON MODIFIED NISHIDA PROCEDURE: A SAFE AND EFFECTIVE TRANSPOSITION MYOPEXY IN VARIED LARGE-ANGLED COMPLEX STRABISM

INTRODUCTION

Transposition procedures are useful procedures in improving duction past midline and at the same time correcting large angle primary position deviation in complex incomitant squints. But weakening the tight antagonist of the paretic muscle is must before any transposition procedure can be planned. In the past authors have described varied transposition procedures including full tendon horizontal or vertical muscle transposition. But recessing the antagonist with full tendon transposition can bear the risk of anterior segment ischemia if done in the same sitting; and procedure does not become safer even when spaced with time. Hence, in the past many authors have described vessel sparing transposition procedure as alternative to full-tendon Transposition. Nishida et al[1] described a no-split, no-tenotomy transposition procedure using nonabsorbable suture in 6th nerve palsy (6thNP) but the vector forces used in the transposition consisted of one-third muscle width. Both modified Nishida and partial tendon transposition are safe alternatives but their efficacy remains low. Published

reports on modified Nishida confirms mean correction of 30pd of deviation.[2,3,4] So, alignment of large-angle squint along with improvement in duction limitation remain a challenge. So, we here aimed to study safety and efficacy of our previously[5] described technique of full-tendon modified Nishida (FTMN) or full-tendon transposition myopexy in correcting large-angle deviation in various complex strabismus.

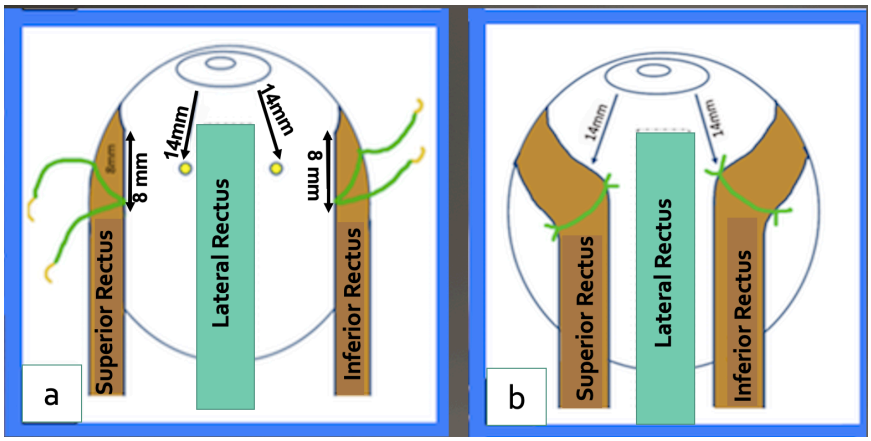
METHODOLOGY

This retrospective cohort study was approved by the Institutional Review Board of our institute and followed the tenets of the Declaration of Helsinki. The medical records of all patients with complex strabismus who underwent squint surgery at our tertiary institute from December 2017-September 2021 were reviewed. Patients of complex strabismus of varied types who underwent FTMN with minimal follow up of 6 months were included in the study. Informed consent was obtained for all patients. Age, sex, any relevant systemic findings, visual-acuity, anterior/posterior segment examination findings were recorded. Complete orthoptic work-up including pre and post-operative measurements of squint, ductions, any face turn, and force duction test were recorded. Deviation was measured by an alternate prism-bar cover test (PBCT), Krimsky, and Hirschberg corneal reflection tests. Ductions were recorded on a scale from 0 to −4, with 0 indicating full rotation up to canthus, −1 for slight limitation, −2 for half the range from the midline to canthus, −3 for slight movement from midline but not up to halfway, and −4 for not crossing the midline.

SURGICAL TECHNIQUE

This described procedure differed from modified Nishida procedure[4,7] in two ways: firstly, the whole width of muscle was transposed without tenotomy or splitting, and secondly, transposition was in the superior quadrant close to

the border of SR. We were able to mobilize the muscle in the desired quadrant and overcome the strong muscle tension by our suturing technique: first two non-absorbable sutures (6,0-dacron) were passed from the central two-third of the two horizontal muscles and secured with knots; scleral marks were then made 12mm from the limbus at the lateral and medial border of SR; needles from the same sutures were then passed from the sclera at the marked site taking horizontal-bites perpendicular to the direction of SR fibers (both sides); same needles while passing out of the sclera were passed from the muscle taking bites from temporal one-third muscle fibers and finally tightened. This technique transposed superior borders of horizontal recti near the lateral and medial border of SR and inferior borders of horizontal recti somewhere near the midpoint in the superolateral and superomedial quadrant (Figure). None of the patients showed signs of anterior-segment ischemia.



Details of the post-operative outcome in terms of correction of deviation along with duction improvement in affected gaze, any sign of anterior segment ischemia (ASI), and resolution/persistence of subjective diplopia were recorded and compared with pre-operative findings

Surgical success was defined as the postoperative alignment ≤10 prism dioptres (pd) and omission of subjective diplopia in primary position.

RESULTS

Operative records of 705 patients who underwent surgeries under general/local anesthesia between July 2017-September 2021 in Advanced Eye Centre, PGIMER were retrospectively reviewed and 22 patients who underwent FTTM were included in the study. Among them 6 patients were pediatric cases. Mean age of 22 patients was 24.41±1.42 years. Among them 10 were congenital and 12 were acquired cases. MRI Brain was done in all acquired patients and only 1 patient had brain stem schwannoma for which patient underwent neurosurgical intervention. Among 22 patients 7 patients had Monocular elevation deficit, 8 patients had 6th nerve palsy, 3 patients had Muscle slippage, 2 patients had Eso-DRS and 2 patients had Exo-DRS. No Anterior segment ischemia was seen in any patient.

MED

Among 7 patients of MED, 2 patients were pediatric cases. Mean age of 7 patients was 21.57 **± 7.28.** There were 6 were male and 1 female. All were congenital cases. Right eye was involved in 6 cases. All had severe ptosis with poor Levator Palpebral Superiororis (LPS) with poor Bells. 2 had severe Marcus jaw winking (MJW). There were 3 patients with history of prior IR recession. All 7 patients underwent FTMN and 3 patients additionally underwent Inferior rectus (IR) recession. M**ean IR recession** in 6 patients was **4.93±0.53** mm. Mean **pre-operative hypotropia was 65.71±20.50pd** and **mean post-operative hypotropia** at the end **6 weeks** and **6 months** was **18.57±7.48** pd (p value<0.01) and **4.29 ±4.82 pd** (p value<0.01) respectively. Mean **pre-op supraduction deficit was -4.29± 0.76 & mean**

post-operative supra-duction at the end **6 months** was **-1.36±0.75** (p value <0.01). 3 patients had additional horizontal deviation in primary position (mean) for which patients underwent recess-resect procedure in contra-lateral eye. **Mean correction** achieved by FTMN alone in 7 MED was **52.57±7.72 pd**.

SIXTH NERVE PALSY

8 patients of 6th Nerve Palsy (mean age 26±18.6 years). All patients were male. All cases acquired were acquired post-traumatic cases except 1 which was acquired due to compressive neuropathy sec to brain stem SOL. Left eye was involved in 5 cases. All 8 patients underwent FTMN and MR recession (mean 5.88±1.36mm). Among 8 patients, there was 1 patient with history of prior MR recession while 5 patients underwent MR recession in the same sitting with FTMN. Mean **pre-op esotropia** in 8 patients was **65.71±20.5 pd** and mean post-operative esotropia at the end of 6 weeks and 6 months was **10.63±9.8 pd** and **2.25± 6.76 pd** respectively.

Mean pre-op and post-operative abduction deficit was **-4.29±0.76** and **-1.36±0.75** respectively (p value<0.01). Mean correction achieved by FTMN alone on temporal side in 6th nerve palsy cases was **41.75±10.43pd.**

LOST MUSCLE

3 patients with slipped medial rectus muscle. 1 patient post trauma, while 2 iatrogenic. Mean pre-op and post operative exotropia **71.67 ± 23.63 and 21.67 ±20.21pd** respectively. Mean pre-op and post-operative adduction deficit **-4.67±0.58 and -3±0**. Mean correction achieved with FTMN on medial side was **51.67±10.41 pd BI**.

EXOTROPIC-DRS

2 patients of Exo-DRS had exotropia of **60pd BI and 65pdBI** respectively with mean abduction limitation of **-5 in each patient**. All underwent LR periosteal fixation and FTMN on lateral side. Aduction limitation improved to **-2 and -2.5** post-operatively. Correction achieved with FTMN on temporal side was **25 and 30pd BI respectively.**

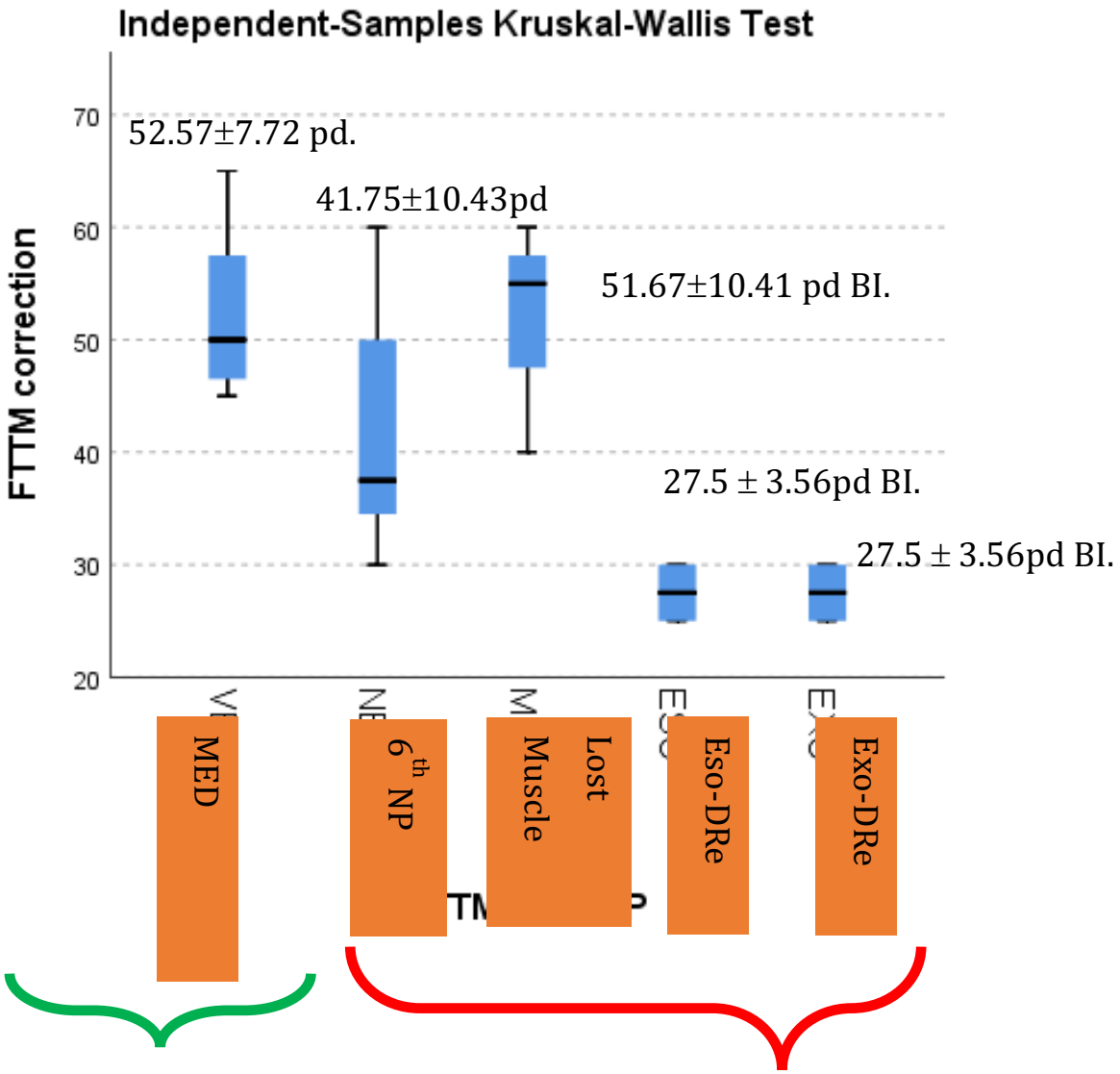
ESOTROPIC –DRS

2 patients of Eso-DRS had esotropia of **45pd BO and 40pdBO** respectively. Mean abduction limitation of **-4** in each patient. Underwent FTMN & MR recession of 4mm and 3.5mm respectively. Abduction improved to **-1** in each patient. Correction achieved with FTMN alone on temporal side **was 30 and 25 pd BO** respectively.

Overall mean correction achieved was 43.95±12.31pd. Correction achieved by horizontal FTMN alone was 39.93±12.13pd and vertical FTMN alone was 52.57±7.72).

Overall p value for FTTM correction among all types of incomitant squint was statistically significant

But applying **Bon-ferrini correction** for multiple comparisons, the **adjusted p value** for every group comparison was not statistically significant.



DISCUSSION

Transposition procedures are generally procedure of choice in presence of duction deficit when eye is not able to cross midline in abducens palsy, monocular elevation deficit, Duane's retraction syndrome and other complex strabismus with an aim to realign eyes in primary position and improve duction. They work by transfer of vector forces of the transposed muscle in the direction of action of the paralyzed muscle. During transposition procedures the muscle pulleys of the horizontal or vertical muscles located

10-12 mm from the globe[6] centre are pulled along the transposed site due to parallel placement of transposed muscles with respect to the paretic muscle thereby producing a powerful ducting force. Their success in improving duction could be attributed to the presence of resting muscle tone or passive restraint of the transposed muscle at the transposed sight which assists in holding the eye in primary position and improve duction during relaxation of its corresponding antagonist. In augmented procedures with posterior fixation sutures, it has been suggested that rectus muscle pulleys are diverted posteriorly in the direction of transposition while translating the centre of the globe. Full tendon transposition procedure with or without posterior fixation suture (Foster)[7] has the maximum potential to correct large angle deviation but bear risk to anterior segment supply specially when combined with weaking of antagonist or in patients with vascular insufficiency.

Hence many procedures with partial tendon transposition have been described in the literature.

Hummelsheim[8] split half-tendon width superior and inferior muscles up to approximately 14 mm from the insertion and sutured transposed halves of both vertical recti are to the sclera adjacent to the insertion of the lateral rectus for the correction of esotropia in sixth nerve palsy. Modification of Hummelsheim procedure[8] by resection of the transposed tendon along with recession of medial rectus has only been reported to correct a preoperative deviation of 43 Δ ± 5 Δ to postoperative 6 Δ ± 7 Δ .(5) A large number of modifications further took place resulting in a large number of variations in the procedure.

In the past many authors have described vessel sparing transposition procedure as alternative to full-tendon. In 2003 Nishida et al transposed

longitudinally split halves of the vertical recti bellies onto sclera close to the lateral rectus without tenotomy in 6thNP.[1] Later they modified their transposition procedure bypassing 5-0 nonabsorbable suture through each temporal margin of vertical recti at one-third width at 8-10 mm behind the insertion and then transposing the lateral margin of each vertical recti taking scleral bites at the midway between vertical recti and LR in the supero-temporal or inferotemporal quadrant at a distance of 10 to 12 mm behind the limbus.[2,3] So, the vector forces involved in their no-split, no-tenotomy transposition procedure consisted of one-third muscle width and mean correction achieved was

But at times with large deviation and duction deficit partial tendon transfer fails to achieve satisfactory post-operative outcome. So we need a full tendon transposition procedure without tenotomy with a posterior fixation suture aimed at diverting muscle pulley more posteriorly in the direction of transposed muscle in order to achieve maximum correction in large angle incomitant squints. We therefore further modified "Modified Nishida" procedure as no-split, no-tenotomy full tendon transposition myopexy and average correction achieved in our study.

VERTICAL FTMN

Vertical FTMN using horizontal recti was performed in Monocular elevation deficit (MED) also known as double elevator palsy. MED is characterized by impaired up-gaze, hypotropia, and ptosis and its surgical correction is warranted before patients undergo ptosis surgery to correct primary position (PP) hypotropia and improve Bells. The choice of surgical procedure depends on the amount of PP hypotropia, inferior rectus (IR) tightness, superior rectus (SR) tug[9] and either IR recession or Knapp's procedure with

or without Foster augmentation is the preferred procedure.[10] The procedure showed marked variability correcting 21-55 PD (average 38 PD) hypotropia.[11] But large PP hypotropia cannot be tackled by IR recession alone and it is often safely combined with partial tendon vertical transposition. But the procedure is ineffective in correcting large-angle residual hypotropia whose optimum correction remains a surgical challenge. Full-tendon transposition of the horizontal muscles along with IR recession is often the surgery of choice but has the potential to compromise anterior-segment supply even if spaced with a duration of 4-months.[12] Full tendon Nishida may be a safer choice with advantage of correcting large residual large vertical deviation after IR recession. In our study correction achieved by **vertical FTMN** alone **was 52.57±7.72) which was comparable to full tendon Knapps with foster.**

HORIZONTAL FTMN

Horizontal FTMN using vertical recti was performed in in complete 6th nerve palsy, Esotropic Duanes, Exotropic Duanes, lost muscle with eye not passing midline. Full tendon vertical muscle transposition also bears risk of Anterior segment ischemia specially if combined with recession of antagonist (tight horizontal muscle) in the same or subsequent setting. Jensen reported a safer procedure in 6th nerve palsy wherein the lateral half of the superior or inferior rectus were joined without tenotomy to the lateral rectus but its effect waned off with time. In 1997, Foster reported that vertical muscle transposition, augmented with lateral fixation sutures, increased abduction force while maintaining adduction in patients with Duane's syndrome or sixth nerve palsy. Also in Exo DRS, improving abduction after supra-maximal recession/periosteal fixation of lateral rectus require transposition procedure and vertical recti transposition may be required in setting of large

consecutive primary position esotropia after the lateral rectus weaking. Partial-tendon transfer being a safe alternative in such situations sometimes may not suffice in the setting of large PP esotropia and large abduction deficit created after LR periosteal fixation. Transposition have been long described in esotropic DRS to correct esotropia in primary position and improve abduction limitation but again full tendon bear risk of ASI with medial rectus recession. Correction achieved in our study by **horizontal FTMN** alone **was 39.93±12.13pd** which was comparable to full tendon VRT.[13] So, in our study, FTMN served as a useful alternative without risk of anterior segment ischemia in all these conditions.

Comparison of correction in various types of incomitant paralytic and restrictive strabismus

Overall correction achieved by vertical FTMN was smaller than vertical FTMN and the reason could be because greater dissection of cheque ligaments were possible on horizontal recti compared to vertical recti and hence better transposition of muscle and its vector with greater correction was achieved.

Correction achieved by esotropic and exotropic DRS was lesser than other types of strabismus. This could be because these were restrictive squints included in the study in which primary position squint hardly correspond with amount of duction limitation. More over values taken for statistical analysis was primary deviation and not secondary deviation and this could explain recorded smaller correction.

CONCLUSION

FTTM is a safe and effective procedure in correction of large-angle incomitant strabismus and improving duction when done in combination with ipsilateral antagonist recession

Without tenotomy this technique displaces the full- thickness pulleys of the bellies and hence the muscle center in the direction of the transposed site which is close to the border of paralysed muscle resulting in greater tonic ducting force.

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This paper was judged as the BEST PAPER of Trauma Session

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D.O.T.S : DOCUMENTING TRAUMA WITH SMARTSCOPE KIT

Eyes represent 0.27% of the total body surface area & are the 3rd common organ affected by injuries.Ocular imaging modality add value to the clinicalcare & are the best evidence to be used in MLC along with documentation and counselling. AIM:To photograph cases of ocular trauma for an ophthalmologist safety in giving prognosis & avoiding problems faced in MLC.We used Smartscope kit -ant & post segm smartphone imaging tools which was used in casualty without slit lamp aid to take photographs to document the nature of ocular injury.350 MLC pts- 3 months- underwent imaging -lid tear2%,SCH,10% corneal tear,26%traumatic cataract,4% hyphema,10% hypopyon,4% lens dislocation,6% commotio retinae,2% IOFB,2%TON 2%,VH 4%,RD6%etc.In court, it is the role to be fair and balanced in the discussion of scientifc evidence, and provide a reasoned explanation,understandable by lay audience. In our study it was easily accomplished with the help of ocular photographs which were taken at the time of trauma.

INTRODUCTION

The eye represents only 0.27% of the total body surface area and 4% of the facial area, but it is the third most common organ affected by trauma after hands and feet [1]. Ocular trauma is a significant public health problem and preventable cause of visual morbidity [1–5]. It is common in developing countries and may lead to permanent visual impairment [1, 2, 4, 6, 7] It may occur at any age in either sex [1, 4], especially among pediatric and elderly population [1]. Both hospital and population based studies indicate a large preponderance of traumas affecting males [1, 2, 4, 7–9]. According to estimates of world health organization (WHO), the global annual incidence of ocular trauma is around 55 million [3, 6, 10, 11] and worldwide blindness in 1.6 million people is due to ocular trauma [1, 7, 11–12]. Corneal tear, sclera tear and lens damage are the most frequently observed morbidities of ocular trauma [1, 2, 11, 13, 14] followed by lid and canalicular laceration, uveal prolapse, anterior chamber (AC) abnormality, retinal detachment and optic nerve avulsion [2, 11, 15, 16]. Majority of the patients were presented in to eye health facilities after 24 hours from time of trauma [1, 2, 3, 5, 6, 13, 17]. Patients reported within 24 hours of eye injury showed better visual outcome as compared to later than 24 hours presentation [2]. Socio-economic burden of ocular trauma is high involving a huge cost in human unhappiness, economic inefficiency and monetary loss [5, 6]. Its direct and indirect costs are known to run into millions of dollars annually [1].

Nevertheless medicolegal cases in such a scenario has been ever increasing and also documentation of the trauma cases becomes very important. Ocular imaging modality add value to the clinical care & are the best evidence to be used in MLC along with documentation and counselling.

AIM: To photograph cases of ocular trauma for an ophthalmologist safety in giving prognosis & avoiding problems faced in MLC.

METHODS

A prospective study was done. We collected the data from Patients attending the emergency/casuality. All the patient underwent examination using smartphone based instruments from the smartscope kit without slit lamp aid to take photographs to document the nature of ocular injury.

The smartscope kit consitis of

- Trial frame, pin hole, +10d lens
- Smartphone visual acuity charts – recording visual acuity, ischiara chart, contrast sensitivity chart
- Anterior Segment Photography with Intraocular lens (ASPI) : for anterior segment evaluation
- Anterior Segment Photography with Intraocular lens gonioscopy (ASPI-gonio) : for anterior chamber angle evaluation
- Trash To Treasure Retcam : for posterior segment evaluation
- Smartphone COaided cObalt Blue photography DO it yOurself (SCOOBY DOO) : for cobalt blue photography to detect epithelial defect, seidels test, dry eye etc
- IOLSCOPE : to detect fungal hyphae from corneal scrapping and parasite from lid/conjunctiva etc
- Schiotz tonometer : to screen for IOP
- Kimuras spatula / 11 blade
- Gloves, cotton swab, fluorescein strips, eye patch, dilating and anesthetic eye drops

Patient were then grouped into their respective specialties for treatment – cataract, cornea, glaucoma, paediatrics, retina and were referred to the base hospital.

RESULTS

350 MLC pts- 3 months- underwent imaging -lid tear2%, SCH,10% corneal tear, 26%traumatic cataract, 4% hyphema, 10% hypopyon, 4% lens dislocation, 6% commotio retinae, 2% IOFB 2%, TON 2%, VH 4%, RD6%

DISCUSSION

One of the major drawback of ophthalmologist as a specialty is that it requires a wide variety of expensive instruments for examination and also for imaging. although slit lamps with cameras are available, it is out of reach for many post graduate, fellows and ophthalmic practitioners. With the introduction of smartphone based frugal do it yourself instruments, this barrier can be removed hence allowing each and every ophthalmic person to take images of anterior posterior microscopic cobalt blue imaging etc and record these for protection against any mlc case, for follow up reasons, for counselling.

CONCLUSIONS

In court, it is the role to be fair and balanced in the discussion of scientifc evidence, and provide a reasoned explanation,understandable by lay audience. In our study it was easily accomplished with the help of ocular photographs which were taken at the time of trauma.

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This paper was judged as the BEST PAPER of Uvea Session

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HOME-MADE DO-IT-YOURSELF AQUEOUS SAMPLING DEVICE FOR ANTERIOR CHAMBER TAP IN ENDOPHTHALMITIS

ABSTRACT:

Rapid diagnosis & treatment is essential for successful management of endophthalmitis. Aqueous tap(AT) can be performed easily & provides useful information. AT using conventional technique, often has inadequate quantity of fluid & decreased possibility of successful bacterial growth. This study describes novel aqueous sampling device (ASD) & compares it with conventional technique of 26G needle on tuberculin syringe.

Forty ~~40~~ patients, who underwent both aqueous & vitreous tap before intravitreal antibiotics/vitrectomy were divided equally in 2 groups. In Group A, AT was done using conventional technique. In Group B, AT was done using the ASD. A positive result meant that pathogen was successfully grown in culture/stain. The ~~R~~ result of AT was also compared to result of vitreous tap to rule out false results.

The Lab returned 9/20 samples in Group I and 5/20 samples in Group II sstating the quantity was not sufficient. Positive result was seen in 3 in Group I as compared to 9 in Group II. Specificity and sensitivity of ASD was higher than conventional method.

INTRODUCTION:

Endophthalmitis is a serious inflammation resulting from infection of the eye. It can be post-operative, post-traumatic, endogenous or secondary to keratitis. Rapid diagnosis and appropriate treatment is required to save the eye from irreversible blindness. Accurate, appropriate and adequate sampling is the key to precise microbiological diagnosis. Culture of intraocular specimens can be obtained from aqueous humor, vitreous humor or vitrectomy fluid. Though vitreous tap and vitrectomy fluid are more sensitive, these have to be performed in an operation theatre by a skilled retina specialist. Considerable time is lost before initiating the treatment leading to further growth of organism inside the eye and cause worsening of condition. Aqueous tap followed by intravitreal injection of antibiotics can be easily performed by a comprehensive ophthalmologist before referring the patient to a retina specialist. Conventional technique of doing aqueous tap using a 26 gauge needle mounted upon a syringe (CSD) is difficult to perform resulting in inadequate sample. We compare a novel home-made Aqueous Sampling Device (ASD) to the Conventional Method (CSD) for collection of aqueous fluid.

MATERIALS & METHODS:

Preparation of Aqueous Sampling Device (ASD); Plunger of a 2 ml syringe is removed and the finger flanges are cut using a scissors. Rubber bulb of a nasal dropper is removed and attached to the cut end of the syringe. This forms the ASD. This can be done on the spot or this device can be sterilised and kept for later use. While in use, a 26-gauge needle is connected to the syringe. The rubber bulb is pressed to create vacuum in the syringe. The needle is then inserted in the anterior chamber and the bulb is released

slowly. The aqueous starts collecting in the syringe due to the suction pressure created in the syringe.

40 clinically diagnosed cases of endophthalmitis who underwent aqueous and vitreous sampling in the retina clinic of a tertiary eye care centre were included in the study. Informed consent was taken for diagnostic procedures, management and clinical trial. Ethical clearance for study was obtained from the Institutional Ethics Committee. Forty cases were equally and randomly divided into 2 groups. In Group A, the aqueous sample was taken by conventional technique of paracentesis using a 26-gauge needle mounted on 1 ml syringe. In Group B, the aqueous sample was obtained using the novel ASD.

The samples were collected by the ophthalmologists in the operation theatre under peribulbar anaesthesia using strict aseptic conditions within 6 hours of presentation. All aqueous taps were followed by a vitreous biopsy using 27-gauge vitrectomy aspiration cutter through sutureless pars plana incision. Intravitreal antibiotics were given in all eyes through the same 27-gauge incision at the end of the procedure.

After the collection of specimen, the needle was capped with a sterile rubber bung or a sterile cap and placed in a sterile test tube. It was sent to the laboratory immediately where the specimens were inoculated immediately on culture media and were processed for direct smear examination by Grams staining. Positive result meant that the organism was detected in either the culture or the gram stain. Result of the aqueous tap was also compared to the result of vitreous biopsy to rule out any false positive results.

RESULTS:

Characteristic	Group A (CSD)	Group B (ASD)
Post-Operative	17	16
Post Traumatic	2	3
Endogenous	1	1
Aqueous Samples Sent	20	20
Quantity Not Sufficient	9	5
Samples Processed	11	15
Positive Result	3 (27.3%)	9 (60%)
Vitreous Biopsy Sent	20	20
Positive Result	15 (75%)	14 (70%)

DISCUSSION:

Early & timely diagnosis and appropriate treatment is essential for successful management of endophthalmitis. Initial management of endophthalmitis may not be dependent on microbiological results but the microbiology is important for subsequent modification of treatment. The initiation of therapy by giving broad spectrum oral or intravitreal antibiotics may alter the sensitivity or specificity of the subsequent fluid sample. It is better to obtain a fresh sample before giving an intravitreal broad-spectrum antibiotic. The various microbiological specimens can be obtained from aqueous tap, vitreous tap/biopsy or vitrectomy fluid. Though vitreous fluid is the best source to obtain a specimen for culture or smear examination, it can be obtained only in the operation theatre under peribulbar anaesthesia by a retina specialist. Valuable time is lost in referring the patient to retina specialist and subsequent shifting of the patient to operation theatre for vitreous biopsy/tap. This may lead to worsening of and irreversible damage to the eye. An aqueous tap with an intravitreal antibiotic injection by the

primary care ophthalmologist before referral could be a better alternative and result in early initiation of therapy after obtaining a fresh aqueous specimen.

Conventionally, the aqueous sample is obtained using a 26-gauge needle mounted on a 1 ml syringe. An assistant holds the eye in position, when the ophthalmologist inserts the needle in the anterior chamber and withdraws fluid into a syringe. This usually results in an inadequate sample and requires an assistant to hold the eye. On using the novel Aqueous Sampling device (ASD), the aqueous sample can be obtained easily without the help of an assistant. The ASD can be prepared immediately or it can be sterilised and kept for a later use.

The results in the current study shows that adequate aqueous sample is obtained and the positivity rate is only slightly less than the vitreous biopsy.

CONCLUSION:

Though Vitreous is the best source for obtaining a specimen for culture or smear examination, the ASD is easy to use and an aqueous sample obtained using it before giving an intra-vitreal antibiotic gives adequate positive results.

This paper was judged as the BEST PAPER of Vitreo Retinal Diseases – I Session

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ROLE OF OCT BIOMARKERS IN DETERMINING TREATMENT OUTCOMES IN RETINOPATHY OF PREMATURITY

Non-contact ultra-widefield swept source optical coherence tomography biomarkers in predicting treatment response to intravitreal anti-vascular endothelial growth factors in aggressive retinopathy of prematurity

KEY WORDS:

OCT Biomarkers, aggressive retinopathy of prematurity, anti-vascular endothelial growth factor

SYNOPSIS:

Baseline non-contact ultra widefield swept source optical coherence tomography biomarkers could predict the treatment outcomes of intravitreal anti-vascular endothelial growth factors (Bevacizumab) monotherapy in aggressive retinopathy of prematurity eyes.

Abstract:

OBJECTIVE:

To illustrate the role of non-contact ultra-widefield swept source optical coherence tomography biomarkers in predicting treatment response to

intravitreal anti-vascular endothelial growth factors (anti-VEGF) Bevacizumab in aggressive retinopathy of prematurity (A-ROP).

METHODS:

Non-contact ultra-widefield (NC-UWF) fundus imaging with integrated UWF guided swept source Optical coherence tomography (SS-OCT) was performed using the Optos Silverstone before and after intravitreal anti-VEGF (Bevacizumab) monotherapy. OCT biomarkers were analysed in eyes that reached complete vascularization versus others.

RESULTS:

Eyes with retinal vessels reaching near ora serrata were labelled as regressed ROP and vascularised retina (Group1). Eyes with reactivation of ROP needing laser or peripheral incomplete vascularization at 16th week post injection or eyes needing vitreoretinal surgery were considered as (Group 2). Pre-injection baseline OCT showed, a hyperreflectivity of inner retinal layers in 12 out of 46 eyes in Group 1 vs 30 out of 34 eyes in Group 2 (p value 0.020). None of the eyes in Group 1 showed choroidal thinning at posterior pole as compared to 14 out of 34 eyes in Group 2 (p value 0.001). Intraretinal hypo reflective Cystic changes at fovea was seen in 16 out of 46 eyes in Group 1 and 2 out of 34 eyes in Group 2 (p value 0.012).

CONCLUSION:

NC-UWF swept source OCT biomarkers before injection can predict the treatment outcomes of anti-VEGF (Bevacizumab) monotherapy in A-ROP eyes. Hyperreflectivity of inner retinal layers and choroidal thinning could indicate poorer and unpredictable response to anti-VEGF injection whereas, cystic changes at fovea could be protective.

INTRODUCTION

Retinopathy of prematurity (ROP) is a time bound Vaso proliferative disease seen in prematurely delivered babies. It can be vision threatening if not diagnosed and treated promptly. Aggressive retinopathy of prematurity (A-ROP) is a severe form of ROP with rapid development of neovascularization that can rapidly progress to retinal detachment if untreated. [1,2] Characteristic features of A-ROP include dilated and tortuous vessels in posterior retina and beyond, shunting of vessels, large areas of avascular retina and extraretinal flat neovascularization. [1,2] Although A-ROP is more common in extremely premature babies with very low birth weight, it can also be encountered in larger preterm babies in regions with lesser resources. [1] Examination by indirect ophthalmoscopy after pupillary dilatation to diagnose and treat ROP has been the standard of care. While laser therapy has been the standard of care for many years. [3,4] In recent times there is a paradigm shift worldwide in treatment of A-ROP with anti-vascular endothelial growth factor (anti-VEGF) inhibitors. [5,6] Several studies have shown anti-VEGF injections to be safe and effective alternative to conventional laser in treatment of A- ROP disease. [7,8,9] Treatment with anti-VEGF injection has much better favourable anatomical outcomes with lesser chances of myopia progression when compared to lasers. [7,8,9] However, anti-VEGF treated eyes have higher chances of late reactivation of ROP needing laser and demands much longer and frequent follow-up visits. [7,8,9]

The advent of faster and high-resolution wide field imaging techniques with neonatal fundus imaging and OCT imaging are currently emerging as important tools for documenting and treatment planning in ROP. [10,11] Recent advances in widefield optical coherence tomography (OCT) imaging techniques are more beneficial in neonatal eyes for capturing macular, peripheral, and vitreoretinal interface images. [11] The faster image acquisition speed and consistent ability to reproduce high resolution OCT

images are some of the advantages of these machines. [11,12] Previous studies have looked at various phases of foveal maturation in eyes of preterm babies with and without ROP. [11,12] In our study we discuss important OCT changes that were associated with the treatment outcomes in post anti-VEGF treated A-ROP eyes. Currently, there are no robust non-invasive ocular markers to predict which eyes post injection will need further intervention. Non-contact OCT imaging-based biomarkers could have an advantage due to being non-invasive, quicker, and safer in neonatal eyes when compared to tears, blood serum and fundus fluorescein angiography-based markers. [13,14,15,16]

MATERIALS AND METHODS

In this prospective study, all systemically stable babies diagnosed with A-ROP by the vitreoretinal faculty at the outpatient department of a tertiary eye care centre from 1st June 2022 to 30th September 2022 were included. They were followed-up for at least 16 weeks till 31st January 2023. The study was approved by the institute review board (LEC-BHR-P-09-22-926) and the study adhered to the tenets of the Declaration of Helsinki. All ROP descriptions and classifications followed the revised ICROP3 (2021) recommendations. [1] All babies were examined with indirect ophthalmoscope after the instillation of topical mydriatic (tropicamide 1% and phenylephrine 2.5%) 3 times at an interval of 10 minutes and topical proparacaine 0.5% once before inserting a paediatric Alphonso lid speculum. The study enrolled 80 eyes of 40 systemically stable babies diagnosed with A-ROP and were subjected to imaging. We excluded babies who were not systemically stable, any form of ROP other than A-ROP, stage 2-3 with elevated extraretinal neovascularization or ridge, babies who had received previous treatment either by laser or anti-VEGF elsewhere and babies with media haze or poor pupillary dilatation in whom imaging was

not possible. Non-contact ultra-widefield (NC-UWF) fundus imaging with integrated UWF guided swept source Optical coherence tomography (SS-OCT) was performed using the Optos Silverstone (model name P200TXE, model number A10750) in the retina diagnostic set up.

The babies were covered with warm clothing and held in the modified 'flying baby position' (Figure 1), with one arm supporting the chest/chin and the other hand supporting the head. The head was supported towards the machine, with visual feedback on the monitor guiding the pupillary alignment and the diagnostic technician captured the images. The minimum pupillary diameter to acquire the images was 2mm and the working distance (patients' eye to front of lens) was 25mm.

Silverstone produces a 200-degree single capture optomap image in <0.4 seconds and enables OCT scanning across the retina and into the far periphery. The OCT light source of 1050nm wavelength, enables deeper tissue penetration up to 2.5mm helping in detailed choroidal imaging. Swept source OCT has a A-scan rate up to 100k cycles/second. The axial and transverse image resolution are <7microns and < 20 microns respectively. OCT ultra-wide field guided extended line scan covering entire macula and beyond including both vascular and avascular retina. This can be positioned centrally within an on-axis optomap image, and it can generate a cross sectional OCT image.

Gestational age, Post menstrual age, birth weight, and baseline blood haemoglobin was recorded for all babies. Baseline NC-UWF fundus image with SS-OCT was captured in all 80 eyes of 40 babies diagnosed with A-ROP. None of the babies developed apnoea, cyanosis, or feed intolerance during or after the procedure. All eyes received intravitreal anti-VEGF (Vascular endothelial growth factor) Bevacizumab 0.4mg/0.015ml on the same day and were asked to review after 1-week. NC-UWF fundus image with SS-OCT

was repeated at 1-week and 3-weeks post anti-VEGF injection. Beyond 3-weeks imaging was not done as it would be difficult to capture these images by flying baby position in bigger babies. Throughout the treatment, the correction of any systemic condition like anaemia, breathing or feeding problems, weight gain, or any intercurrent infections were monitored and counselled to care givers in coordination with the treating neonatologist. The babies were followed-up till a duration of at least 16 weeks post anti-VEGF injection and the frequency of follow-up visits were as per the treating vitreoretinal faculty taking into consideration the disease severity and systemic parameters. Treatment outcomes were divided into two groups during follow-up. Eyes with vessels reaching a zone within 1 to 1.5 disc diameter from the temporal ora serrata post anti-VEGF monotherapy were labelled as regressed ROP with vascularized retina (Group1). Eyes with reactivation of ROP post anti-VEGF treatment during follow-up or peripheral incomplete vascularization of retina at 16th week post injection or any eye needing vitreoretinal surgery were considered as (Group 2). Eyes with disease reactivation or with incomplete vascularization at 16th week post injection underwent laser indirect ophthalmoscope. Most of the previous studies show that the mean interval between intravitreal bevacizumab and retreatment for reactivation was between 12 to 16 weeks post injection. [17,18,19] This was the rationale for considering 16th week post anti-VEGF as the timeline for our additional procedure in eyes that showed reactivation or incomplete vascularization. Reactivation is defined as re-emergence of plus disease, progression of retinal neovascularization, new extraretinal fibrovascular proliferation and new preretinal haemorrhage. [17,18,19] OCT biomarkers pre-injection were analysed in eyes that reached complete vascularization (group 1) versus others (group 2) at the end of the study as shown in Figure 2 (Flow diagram of the study design).

Statistical analysis: The OCT changes at baseline (pre-injection) and their strength of association in predicting which eyes will enter Group I or II were analysed. The 2-sample proportion test was used to test the statistical significance of the mean difference between the two groups. A p value of < 0.05 was considered statistically significant. All analysis were performed using the statistical software R Core Team (2020). (R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS:

All 80 eyes of 40 babies diagnosed with A-ROP underwent baseline NC-UWF fundus imaging with integrated SS-OCT. The overall mean gestational age for these 40 babies was 30 weeks (Range 28 to 34 weeks), mean post menstrual age at presentation was 35 weeks (Range 32 to 38 weeks), and the mean birth weight was 1345 grams (Range 890 to 2000 grams) respectively. 46 eyes of 23 babies on indirect ophthalmoscopy examination with indentation showed fully vascularised retina with anti-VEGF monotherapy (Group 1) at a mean duration of 12 weeks post anti-VEGF injection. Remaining 34 eyes of 17 babies needed additional treatment (Group 2) with laser indirect ophthalmoscope in 29 eyes and vitreoretinal surgery with endolaser in 5 eyes. 17 eyes needed laser due to ROP reactivation and the mean duration at which reactivation occurred was at 12 weeks post injection. 12 eyes showed incomplete vascularization at 16th week of follow-up and underwent laser. None of the babies were lost to follow-up. 5 eyes developed crunch phenomenon post anti-VEGF injection needing vitreoretinal surgery. 2 eyes of one baby had developmental cataract post anti-VEGF injection needing lens aspiration.

Table 1: Baseline non-contact ultra-widefield fundus imaging with integrated swept source optical coherence tomography (OCT) biomarkers in aggressive retinopathy of prematurity (A-ROP):

OCT Biomarker (Total 80 eyes)	Group 1 outcome (n= 46 eyes) Vessels reached near to Ora with Anti-VEGF monotherapy	Group 2 outcome (n=34 eyes) 17 eyes showed ROP reactivation, 12 eyes showed incomplete vascularization and 5 eyes showed crunch phenomenon.	P value (Group1 Vs Group 2)
Hyperreflectivity of inner retinal layers Suggestive of ischemia (n= 42)	12 out of 46 (26.08%)	30 out of 34 (88.23%)	0.020
Hypo reflective intraretinal cystic foveal changes (n=18)	16 out of 46 (30.78%)	2 out of 34 (5.88%)	0.012
Choroidal thinning at posterior pole (n=14)	0	14 out of 34 (41.17%)	0.001
Hyperreflectivity of inner retinal layers with choroidal thinning suggestive of severe ischemia (n=14)	0	14 out of 34 (41.7%) 5 of these 14 eyes had developed crunch phenomenon	0.001

Vitreoretinal interface traction at baseline was not seen in any of the eyes. Hyperreflectivity of inner 6 retinal layers including the outer nuclear, outer plexiform, inner nuclear, inner plexiform, ganglion cell layer and the internal limiting membrane suggestive of macular ischemia was assessed. This was observed in the UWF-SS OCT of 42 out of 80 eyes with A-ROP. Out of this 12 out of 46 eyes in Group 1 and 30 out of 34 eyes in group 2 had hyperreflectivity of inner retinal layers of the macula in the baseline OCT. **(Figure 3 and Figure 4)** Intraretinal hypo reflective cystic changes at fovea was observed in 18 out of 80 eyes with A-ROP. Out of these 16 eyes were from Group 1 **(Figure 5)**. Choroidal thinning at the posterior pole was observed in 14 eyes, all of which were from Group 2. All 14 eyes with choroidal thinning at posterior pole also had hyperreflectivity of inner retinal layers suggestive of severe ischemia. 5 of these 14 eyes with both choroidal thinning with hyperreflectivity of inner retinal layers developed crunch phenomenon post anti-VEGF injection needing vitreoretinal surgery **(Figure 3)**. None of the eyes which developed crunch phenomenon had pre-existing fibrovascular proliferation or traction. Moreover, eyes with inner retinal layer hyperreflectivity showed slower vascular progression post anti-VEGF injection **(Figure 4 and Figure 6)**.

Table 2: Comparison of neonatal systemic factors between babies attaining Group 1 and Group 2 outcomes:

Systemic factors	Group 1 (n=23 babies)	Group 2 (n=17 babies)	P value (Group1 vs Group 2)
Gestational age in weeks	31 ± 31.5	30 ± 30.5	0.839

Post menstrual age in weeks	36 ± 36.5	35 ± 35.5	0.912
Birth weight in grams	1405 ± 1432	1280 ± 1301	0.102
Blood haemoglobin in gm/dl	10.0 ± 10.4	8.6 ± 9.0	0.089

The mean gestational age in babies attaining Group 1 and Group 2 outcomes was 31 weeks and 30 weeks respectively. Similarly, the mean post menstrual age at presentation was 36 weeks in Group1 and 35 weeks in Group 2. The mean birth weight of babies attaining Group 1 outcome was 1405 grams and Group 2 outcome was 1280 grams. 20 out of the 40 babies had haemoglobin less than 10 gm/dl at presentation which needed correction by transfusion or haematinics. Out of this 8 of them attained Group 1 outcome and 12 of them attained Group 2 outcome. The mean haemoglobin in babies attaining Group1 and Group 2 outcomes were 10.0 gm/dl and 8.6gm/dl respectively.

DISCUSSION:

In recent years many studies are looking into novel biomarkers that could help in early ROP detection and predicting the ROP outcomes during treatment and follow-up. [13,14,15,16] The major studies in this regard are the ones looking at various non-invasive tear based biochemical markers and invasive blood serum based biochemical markers. [14,15,16] The other spectrum would be the prediction of progression or regression of ROP based on fundus imaging and fundus fluorescein angiography-based markers in eyes treated with anti-VEGF or laser.[13] Previous studies with spectral domain OCT performed by handheld machines have tried looking in to foveal and macular changes, and changes at junction of avascular and vascular

retina in ROP babies. [12,20,21] Maldonado et al showed that cystoid macular oedema was a common macular OCT finding among preterm babies and was not associated with ROP severity. [20] Apart from very few studies, there is a large lacuna in literature regarding novel OCT based changes and their correlation with the outcome to anti-VEGF in eyes with AROP. The present work attempted to explore the same.

There is an increase in detection of eyes with A-ROP in recent years predominantly due to the increase in survival of extremely preterm babies with very low birth weight. [1,2,3,4] Even larger babies are known to present with A-ROP in regions with lesser resources. [1] Similarly there is a paradigm shift in treatment of A-ROP eyes with anti-VEGF considering various favourable anatomical outcomes and delaying the need for laser in babies who are extremely fragile to withstand long hours of laser. [5,6,7,8] Hence in our study we have investigated various OCT based biomarkers at baseline in anti-VEGF treated A-ROP eyes that could predict the chances of reactivation, the chances of unpredictable vitreoretinal interface abnormalities and predicting the eyes needing more frequent and closer follow-up as seen in Group 2 outcomes. The Optos Silverstone can capture non-contact ultra-widefield images with very fast image acquisition speed, higher resolution with enhanced depth of imaging and is very safe in neonates. In our study we found that anti-VEGF treated A-ROP eyes with hyperreflectivity of inner retinal layers in baseline (pre-injection) OCT had unfavourable outcomes necessitating a much higher chances of additional laser treatment or vitreoretinal surgery **(Figure 3 and Figure 4)**. Although this OCT biomarker has not been investigated by any previous study for ROP eyes, we believe this finding could be a parameter of the ischemic load in A-ROP eyes similar to the association of this finding in adult eyes with ischemic central retinal vein occlusion, impending central retinal artery occlusion or ischaemic diabetic

macular oedema. [22,23,24] Another important OCT biomarker depicting ischemic load is choroidal thinning and this has been reported previously in association with increasing ROP severity in eyes with thinner choroid especially the sub foveal choroidal thickness which is affected the most. [25,26] The choroid provides oxygen and nutrient supply to outer retinal layers and thinning at posterior pole suggests ischemia. [25,26] In our study there was a statistically significant association of Group 2 outcomes with these 2 OCT biomarkers. The combination of both hyperreflectivity of inner retinal layers and choroidal thinning at posterior pole could suggest much more severe ischemia and high chance of unpredictable response post anti-VEGF like the crunch phenomenon seen in 5 of the 14 eyes in our study **(Figure 3)**. Although Maldonado et al in their study showed that cystoid macular oedema was not associated with ROP severity, in our study we found a statistically significant association with Group 1 outcome wherein anti-VEGF monotherapy helped in complete retinal vascularization and hence could be a protective biomarker **(Figure 5)**. [20] Among the systemic factors including gestational age, postmenstrual age at presentation, birth weight and blood haemoglobin, in our study we found anaemia to be the strongest systemic factor in association with Group 2 outcome and this has been reported in previous studies. [27,28] Hence we believe anaemia correction should be an integral part of ROP management for favourable outcomes. The prospective nature of this study, the usage of non-contact Ultra-widefield swept source OCT imaging device and accurate novel OCT biomarkers helping in predicting the outcomes to anti-VEGF treated A-ROP eyes are the merits of this study. The limitations of this study are the smaller sample size and need for a stable systemic course in neonates for capturing the image. Additionally, imaging was not feasible in larger babies in follow up. Systemic factors of the baby could have certain amount of influence on treatment

outcomes. The OCT biomarkers were more of qualitative and exact quantification at each area for comparison between groups was not possible as it is difficult to capture same line scan for same area of interest in macula or fovea of all babies since these babies do not fixate at the target during imaging. However, line scan through any area of the macula gives significant clue regarding the presence of OCT biomarkers representing ischemia. The outcomes have been studied for Bevacizumab and not for other types of intraocular injections in A-ROP. Future studies could be done with other types of injections and comparison of FFA, OCT and Tear based biomarkers in the same baby.

SUMMARY

What was known Before: The advent of faster and high-resolution wide field imaging techniques with neonatal fundus imaging and optical coherence tomography imaging are currently emerging as important tools for documenting and treatment planning in retinopathy of prematurity.

What this study adds: Non-contact ultra widefield swept source optical coherence tomography biomarkers before intravitreal injection can predict the treatment outcomes of intravitreal anti-vascular endothelial growth factor (Bevacizumab) monotherapy in aggressive retinopathy of prematurity eyes. The OCT biomarkers suggestive of macular ischemia like hyperreflectivity of inner retinal layers and choroidal thinning at posterior pole should alarm the treating ophthalmologist regarding the chances unfavourable course, reactivation, slower vascular progression, need for retreatment with laser and need for frequent follow-up post intravitreal anti-VEGF in A-ROP eyes.

CONCLUSION

This study identified few changes in non-contact ultra-widefield swept source OCT to be associated with increased requirement of re treatment following intravitreal anti-VEGF for A-ROP. The important ones include hyperreflectivity of inner retinal layers and choroidal thinning at posterior pole suggestive of macular ischemia that are associated with poorer and unpredictable response to anti-VEGF injection. Whereas hypo reflective intraretinal cystic foveal changes at baseline were seen more often in eyes with a higher rate of regression post anti-VEGF. The OCT biomarkers suggestive of macular ischemia should alarm the treating ophthalmologist regarding the chances of unfavourable course, reactivation, slower vascular progression, need for retreatment with laser and need for frequent follow-up post intravitreal anti-VEGF in A-ROP eyes.

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Table 1: Baseline non-contact ultra-widefield fundus imaging with integrated swept source optical coherence tomography (OCT) biomarkers in aggressive retinopathy of prematurity (A-ROP)

OCT Biomarker (Total 80 eyes)	Group 1 outcome (n= 46 eyes) Vessels reached near to Ora with Anti-VEGF monotherapy	Group 2 outcome (n=34 eyes) 17 eyes showed ROP reactivation, 12 eyes showed incomplete vascularization and 5 eyes showed crunch phenomenon.	P value (Group1 Vs Group 2)
Hyperreflectivity of inner retinal layers Suggestive of ischemia (n= 42)	12 out of 46 (26.08%)	30 out of 34 (88.23%)	0.020
Hypo reflective intraretinal cystic foveal changes (n=18)	16 out of 46 (30.78%)	2 out of 34 (5.88%)	0.012
Choroidal thinning at posterior pole (n=14)	0	14 out of 34 (41.17%)	0.001
Hyperreflectivity of inner retinal layers with choroidal thinning suggestive of severe ischemia (n=14)	0	14 out of 34 (41.7%) 5 of these 14 eyes had developed crunch phenomenon	0.001

Table 2: Comparison of neonatal systemic factors between babies attaining Group 1 and Group 2 outcomes:

Systemic factors	Group 1 (n=23 babies)	Group 2 (n=17 babies)	P value (Group1 vs Group 2)
Gestational age in weeks	31 ± 31.5	30 ± 30.5	0.839
Post menstrual age in weeks	36 ± 36.5	35 ± 35.5	0.912
Birth weight in grams	1405 ± 1432	1280 ± 1301	0.102
Blood haemoglobin in gm/dl	10.0 ± 10.4	8.6 ± 9.0	0.089

FIGURE LEGENDS:

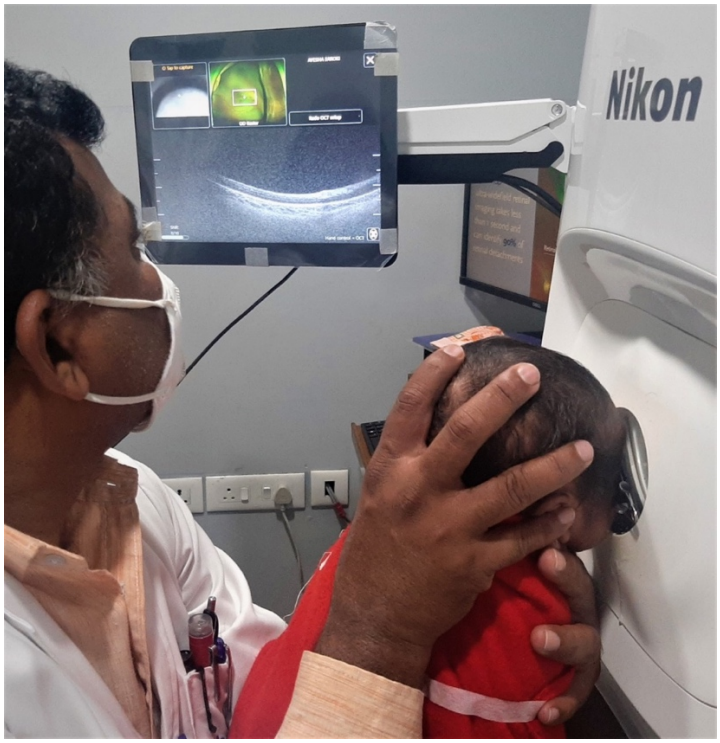
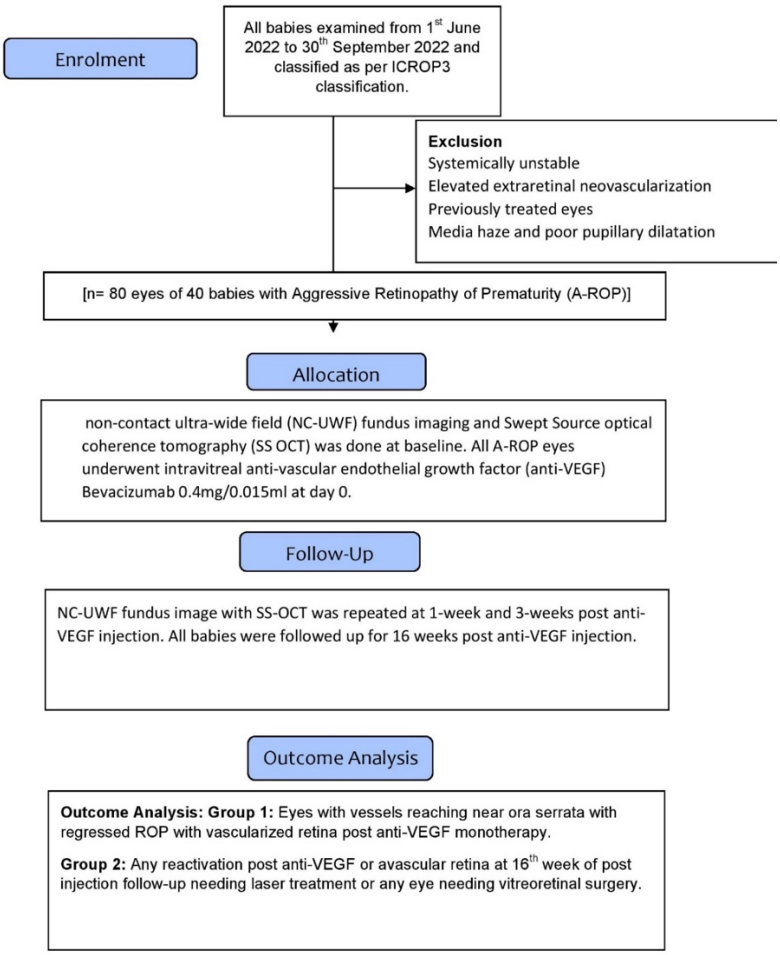


Figure 1: The babies were covered with warm clothing and held in the modified 'flying baby position', with one arm supporting the chest/chin and the other hand supporting the head. The head was supported towards the machine, with visual feedback on the monitor guiding the pupillary alignment and the diagnostic technician captured the images. Silverstone produces a 200-degree single capture optomap image in <0.4 seconds and enables OCT scanning across the retina and into the far periphery.

Figure 2: Flow diagram of the study design.

Figure 2: Flow Diagram of the study design



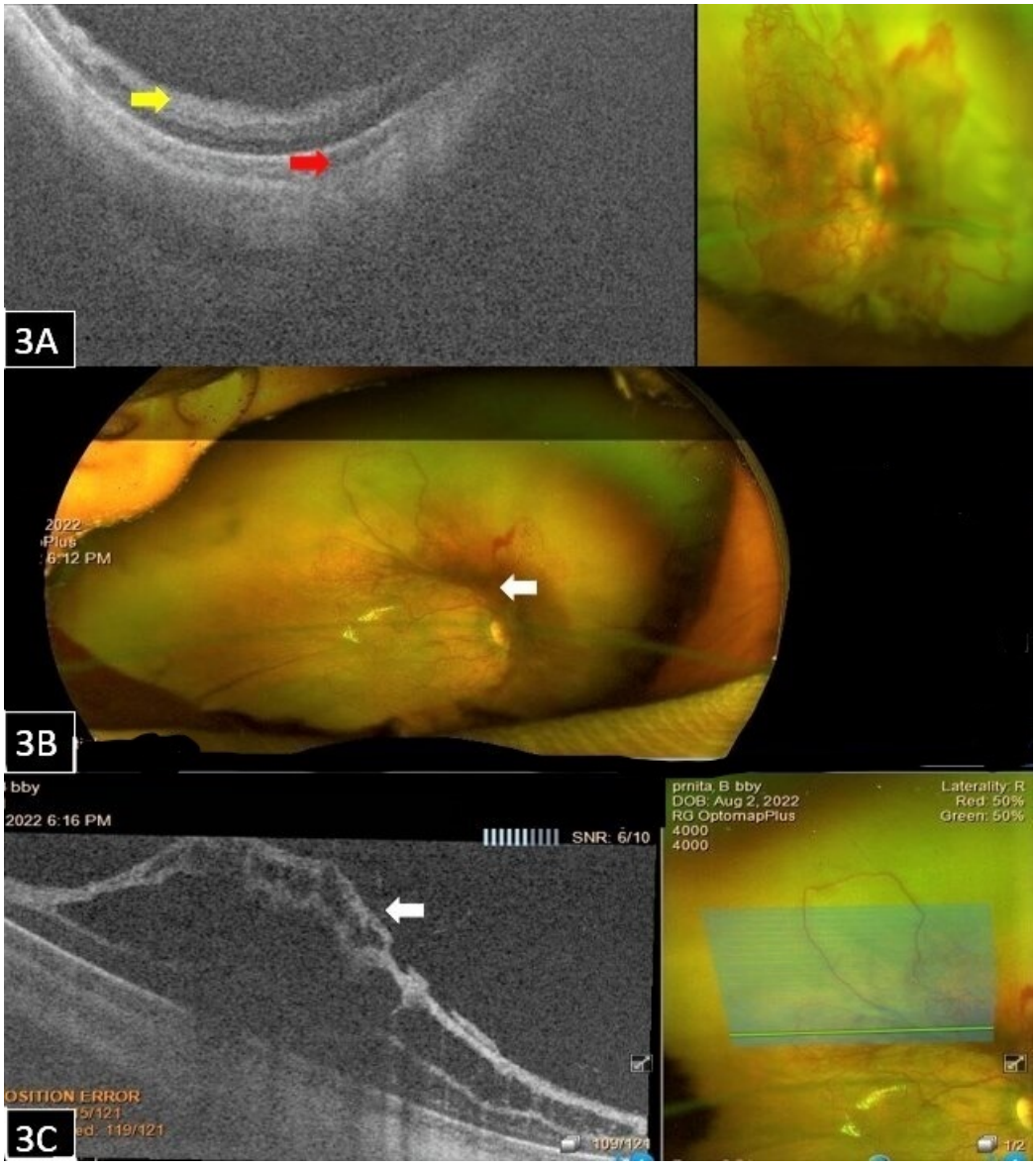


Figure 3: Figure3A showing right eye ultra-wide field swept source OCT (UWF SS-OCT) guided horizontal line scan of a baby with A-ROP with extensive looping and shunting of vessels in zone 1 and incomplete foveal vascularization. The OCT shows inner retinal layer hyperreflectivity across the horizontal line scan (yellow arrow) and significant choroidal thinning (red arrow). Figure 3B shows ultra-wide field fundus photo 1-week post anti vascular endothelial growth factor injection showing crunch phenomenon with fibrovascular proliferation causing tractional retinal detachment at the arcades and nasal to disc (white arrow). Figure 3C shows corresponding UWF-SS OCT guided line scan showing vitreomacular traction (white arrow).

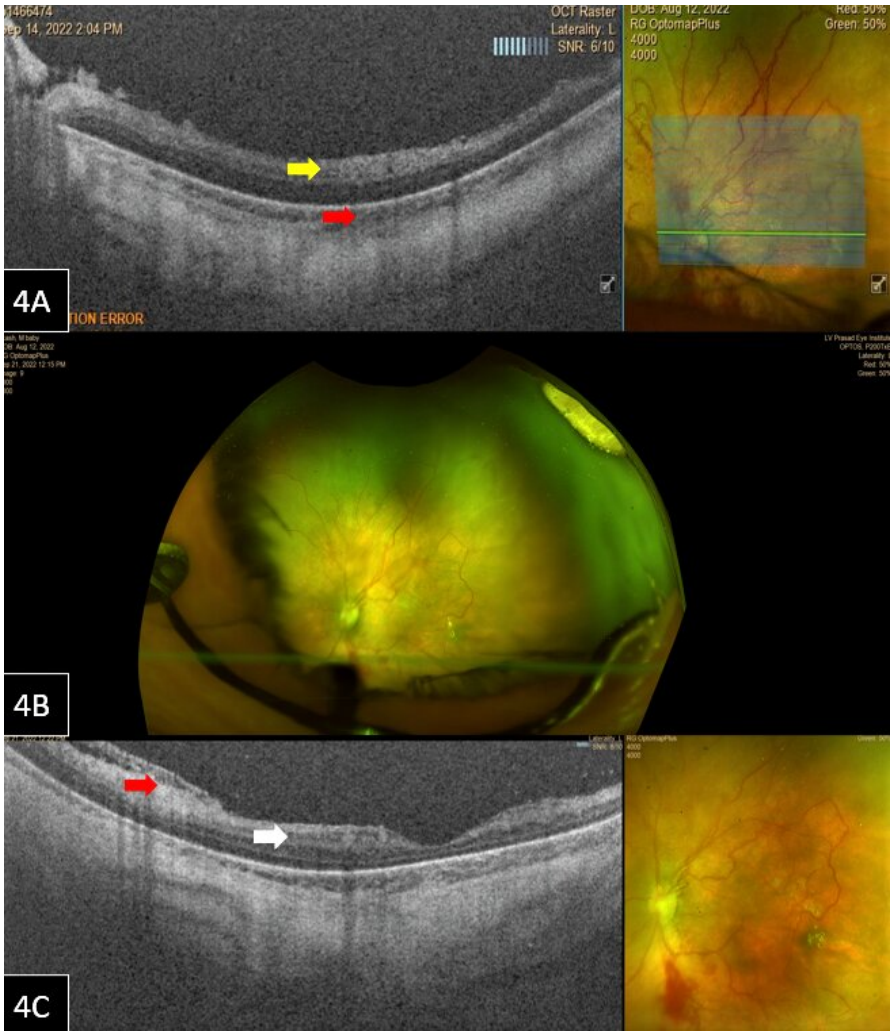


Figure 4: Figure 4A showing left eye ultra-wide field swept source OCT (UWF SS-OCT) guided line scan of a baby with A-ROP with extensive looping and shunting of vessels in zone 1 and incomplete foveal vascularization. The OCT shows inner retinal layer hyperreflectivity across the horizontal line scan (yellow arrow) and significant choroidal thinning (red arrow). Figure 4B shows ultra-wide field fundus photo at 3-weeks post anti vascular endothelial growth factor injection showing reduced plus with slow vascular progression and vessels still in zone 1 with few persisting loops. Figure 4C shows corresponding UWF-SS OCT guided line scan with reducing inner retinal layer hyperreflectivity near the foveal centre (white arrow) but

persisting away from foveal centre with mild vitreoretinal interface disturbance (red arrow).

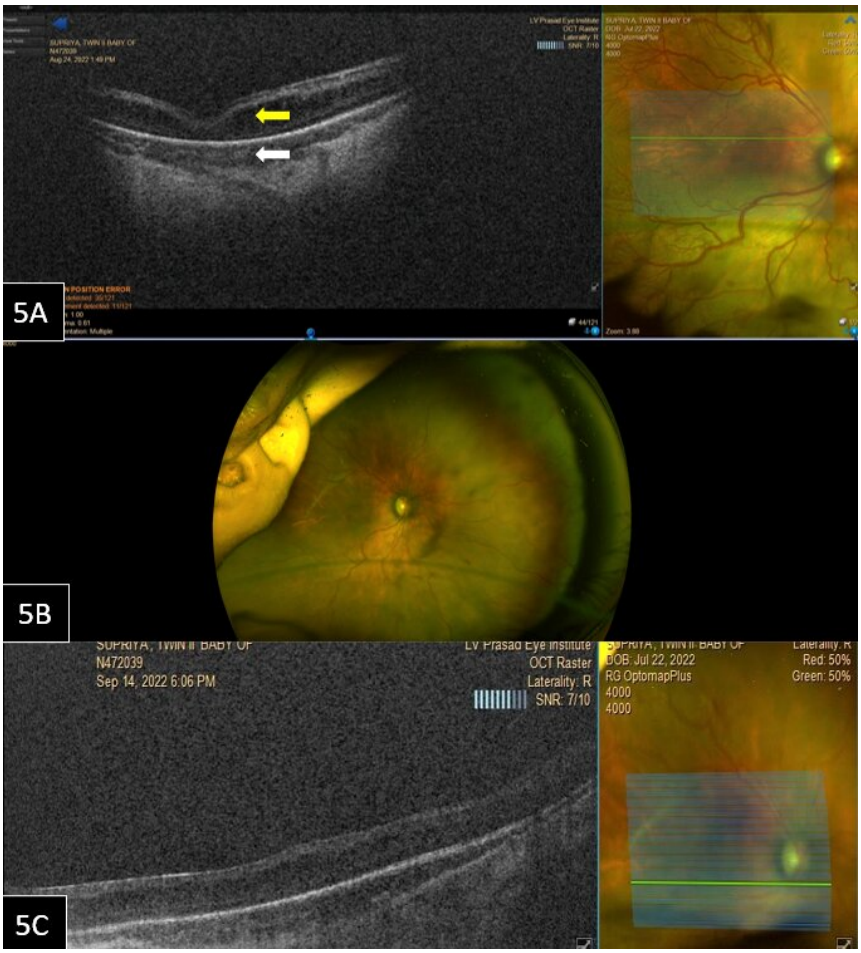


Figure 5: Figure5A showing Right eye ultra-wide field swept source OCT (UWF SS-OCT) guided line scan of a baby with A-ROP with dilated and tortuous vessels with extensive flat neovascularization and few shunt vessels. The OCT shows hypo reflective intraretinal cysts (yellow arrow) and choroidal thickness is better (white arrow). Figure 5B shows ultra-wide field fundus photo at 3-weeks post anti vascular endothelial growth factor injection showing reduced plus with rapid vascular progression and vessels reaching zone 3. Figure 5C shows corresponding UWF-SS OCT guided line scan with resolution of cysts at 3-weeks post injection.

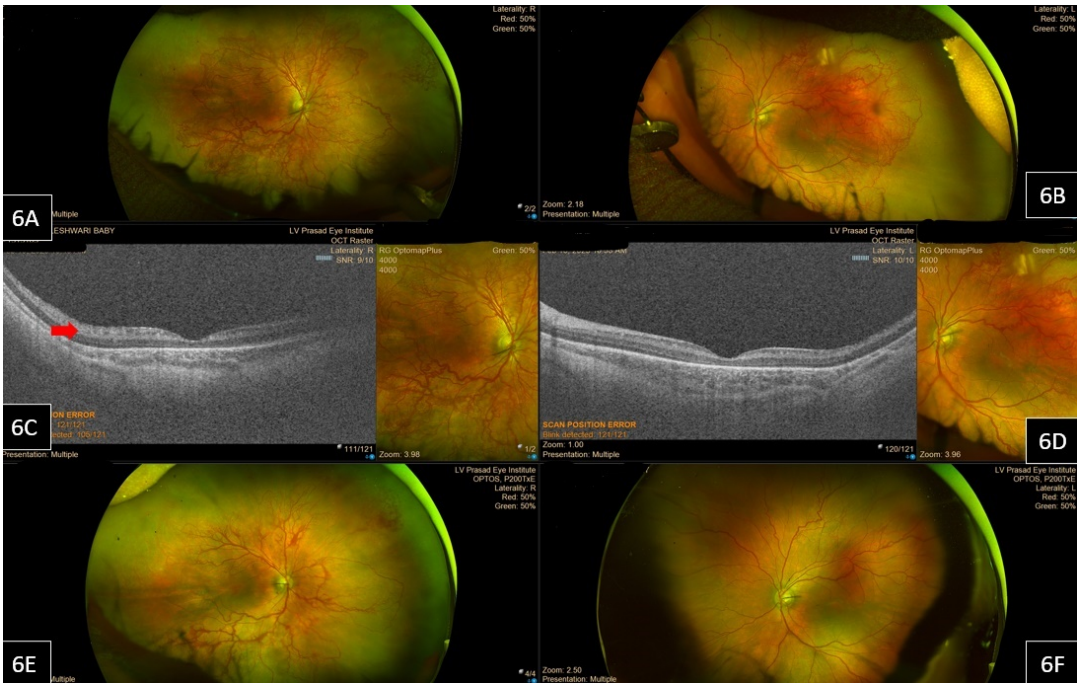


Figure 6: Figure 6A (right eye) 6B (left eye) ultra-wide field fundus image of the same baby showing extensive looping and shunting of vessels in zone 1. Figure 6C (right eye) ultra-wide field swept source OCT (UWF SS-OCT) guided line scan of same baby showing significant inner retinal layer hyperreflectivity across the horizontal line scan (red arrow) in right eye compared to figure 6D (left eye). Figure 6E (right eye) and figure 6F (left eye) ultra-wide field fundus photo at 3-weeks post anti vascular endothelial growth factor injection showing reduced plus with slow vascular progression and vessels still in zone 1 with few persisting loops in right eye whereas vessels are reaching zone 2 anterior in left eye.

This paper was judged as the BEST PAPER of Vitreo Retinal Diseases – II Session

DR. JIZ MARY SANTHOSH J19562

Giridhar Eye Institute, Cochin

OUTCOMES OF VITRECTOMY IN TERSON SYNDROME IN A TERTIARY CARE CENTRE IN SOUTH INDIA

AIM:

To study the outcomes of vitrectomy in non-resolving vitreous hemorrhage in Terson syndrome.

METHODS:

Sequential cases of Terson syndrome from 2007 – 2021 were retrospectively analysed. Patients who underwent vitrectomy were studied in terms of comparison of baseline visual acuity (VA) and VA 1 month post-surgery and final visual outcome. The age, etiology of intracranial haemorrhage, timing of surgery were analysed to see if it affected the final visual outcome.

RESULTS:

33 eyes of 31 patients (age 22-73) with Terson syndrome were analysed, out of which 18 eyes (age 24- 73) underwent vitrectomy. The mean time interval between intracranial hemorrhage and time of surgery was 108.78 days. The mean post op VA 1 month after vitrectomy was significantly higher than the baseline visual acuity (P = 0.001). The age, etiology, and timing of surgery did not affect the final visual outcome of the patient.

CONCLUSION:

Vitrectomy yields exemplary outcomes for non-resolving vitreous hemorrhage in Terson syndrome which were also maintained over a period of time.

INTRODUCTION

Terson syndrome (TS) is defined as intraocular hemorrhage in the setting of an acute intracranial bleed resulting in elevated intracranial pressure(ICP). The earliest definitions meant vitreous hemorrhage (VH) in the setting of subarachnoid hemorrhage (SAH). Now the TS more broadly encompasses intraocular hemorrhage (VH, sub hyaloid hemorrhage, subretinal hemorrhage, or even sub-ILM bleed in the setting of SAH, intracerebral bleed of traumatic brain injury.

It could be unilateral or bilateral. Though various hypotheses exist, the most consistent theory is that elevated ICP impedes ocular venous drainage causing sudden venous hypertension and rupture of retinal vessels resulting in a bleed into the eye.

Treatment options include observation in mild cases which can result in spontaneous resolution and vitrectomy in severe cases causing significant visual loss.

Due to the associated systemic morbidity, there can be a delay in diagnosis of the ocular hemorrhage and also a delay in surgical intervention in the setting of non-resolving VH (NRVH).

This study aims to analyse the outcomes of vitrectomy in NRVH in TS. It also analyses the association of baseline visual acuity, etiology and timing of surgery to the final visual outcome.

MATERIALS AND METHODS

Study Design:

This was a retrospective review of electronic medical records (EMR) conducted on consecutive cases of TS who underwent pars plana vitrectomy at Giridhar Eye Institute, Cochin, Kerala from 2014 to 2021.

Patients were identified using the EMR. All patients with intraocular hemorrhage in conjunction with intracranial bleeding were included irrespective of the etiology. Patients with other potential causes of ocular hemorrhage including ocular trauma, orbital fractures, diabetic retinopathy, or any proliferative retinopathy predisposing to ocular hemorrhage were excluded. Comprehensive ocular examinations were performed preoperatively and throughout the postoperative follow-up period. In cases in which retinal examination was limited, B-scan ultrasonography was used to confirm vitreous hemorrhage and rule out retinal detachment. Data collected included sex, age at diagnosis, cause of

intracranial hemorrhage, best-corrected visual acuity (BCVA), risk factors for intracranial hemorrhage, the period between presentation and vitrectomy, and any surgical complications. Best-corrected visual acuity was measured using Snellen charts and converted to logarithm of the minimum angle of resolution (log- MAR) for analysis. Postoperative data collection was defined by three-time points, 1 week (post-op visit 1), 1 month (post-op visit 2), and 3 months /last follow up whichever is later.

The primary outcome of interest was the change in BCVA from baseline (preoperative) to post-op visit 3. Secondary outcomes included a comparison of final BCVA associated with the timing of vitrectomy (more than or less than 90 days). Also the final BCVA association the age (more than or less than 50 years) was made. The association of etiology and final BCVA was also studied

Although there is no consensus on the timing of vitrectomy, evidence suggests the 90-day cut-point to represent an adequate amount of time for

observational therapy in addition to facilitating comparisons of outcomes across studies.

STATISTICAL ANALYSIS

Results of continuous variables are expressed as mean and standard deviation and that of categorical variables are reported as counts and percentages. Fisher's exact test was used to find the association between the categorical variables. Paired t-test and Wilcoxon tests were used to find the difference between quantitative variables

RESULTS

Thirty-three eyes of 31 patients (age 22-73) with Terson syndrome were analysed, out of which 18 eyes (age 24- 73) underwent vitrectomy. The baseline patient characteristics are given in Table 1.

The mean age of patients at presentation was 46.89 ± 13.12. Fourteen patients were male (77.8%), and four were female (22.2%). All patients sustained SAH, resulting in vitreous hemorrhage; of them 10 were due to road traffic accidents (RTA), and 8 were due to cerebral aneurysm. Among the patients having an aneurysm or vascular malformations, 4 patients had anterior communicating artery (ACA) aneurysm, 2 had middle cranial artery (MCA) aneurysm, 1 had internal carotid artery (ICA) aneurysm, 1 had a vertebral artery dissection. The mean time between the event (motor vehicle accident or aneurysm) and vitrectomy was 108.78 ± 65.932 days. Baseline BCVA was log MAR 1.89± 0.568.

Table 1: Baseline characteristics of patients

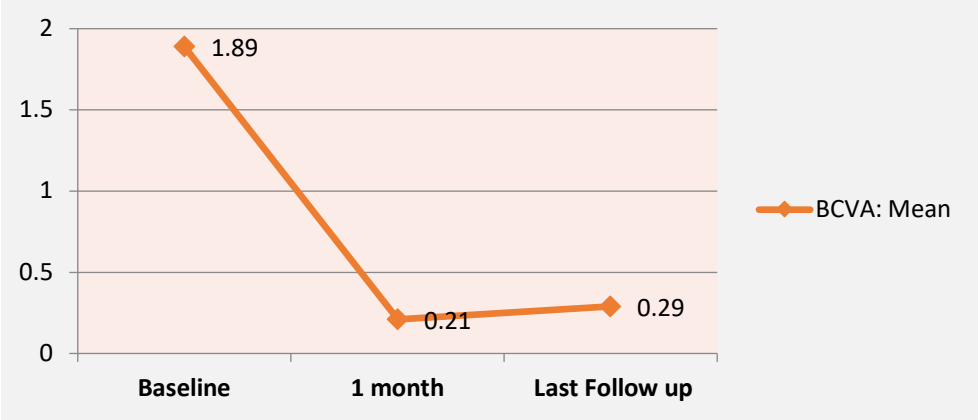
No. of patients	18
Male	14
Female	4
No. of eyes	18
Right eye	12 (66.7%)
Left eye	6 (33.3%)
Mean age (years) ± SD	46.89 ± 13.199
BCVA baseline logMAR Mean ± SD	1.89 ± 0.568
BCVA 1 month logMAR Mean ± SD	0.21 ± 0.210
BCVA Final follow up logMAR Mean ± SD	0.29 ±0.269

Table 2 summarises the age, etiology, and visual outcomes of post-vitrectomy in the included eyes.

Table 3 shows the change in mean BCVA from baseline to 1 month post-surgery and the last follow up. There was a significant improvement in visual acuity 1 month post-vitrectomy compared to baseline visual acuity($p<0.001$).

Table 3 : BCVA – Descriptive Statistics

BCVA	Mean	Std. Deviation
Baseline BCVA	1.89	0.568
BCVA 1month	0.21	0.210
BCVA Last Follow up	0.29	0.269



there were no complications noted during vitrectomy and none of the patients needed a re-surgery.

Further analysis showed that There was no association between baseline visual acuity and final visual acuity. There was no association between the etiology and final visual outcome. There was no association between the age (more or less than 50 years) and the final visual outcome.

DISCUSSION

In our study , the favourable visual outcomes were shown in patients with Terson's syndrome who underwent vitrectomy due to NRVH. There was significant improvement in visual acuity 1 month post-operatively and with a mean follow up of 3 months , there was no drop in visual acuity among the cases. There were no surgical complications or requirement for re-surgery in any of the patients. The systemic morbidity more often resulted in long interval between presentation and timing of surgery. The same was more often a reason for limited follow up of these cases postoperatively beyond 3 months. Though most studies showed that anterior communicating artery aneurysm causing SAH was the most common cause amoung vascular causes, we had patients with ACA , MCA and ICA aneurysm and one patient with vertebral artery dissection. The etiology of RTA or aneurysm did not

seem to be associated with the baseline or the final visual outcome. There are several studies which have shown that timing of surgery had an association with the final visual outcome probably due to the deleterious effects of heme on the nervous tissue. However, our study did not show such an association. The time period of 90 days was decided arbitrarily based on previous studies and review of literature. This could be because of the good neural integrity and function prior to the insult and the vision being compromised only due to the ocular bleed.

Cataract post vitrectomy was noted in one of the patients and this was cleared with cataract surgery later.

More rapid visual recovery post vitrectomy could make the quality of life better in these patients. Further consensus to promote earlier vitrectomy is to avoid complications related to the ocular hemorrhage such as cataract , hemosiderosis , ghost cell glaucoma , epiretinal membrane formation, proliferative vitreo- retinopathy changes etc. Though out study did not show any findings of ERM intraoperatively , even in patients who were operated after 3 months , it seems prudent to opt for an earlier surgical intervention in certain cases.

TS being a rare syndrome, our study is limited by its small sample size. In addition the surgeries were performed by three different surgeons , thereby limiting procedural standardisation. Due to the neurological comorbidities , many patients were lost to follow up beyond the 3 month period and this limits the long term analysis of these patients.

CONCLUSION

Vitrectomy is a safe and effective option in cases of non-resolving vitreous hemorrhage in Terson's syndrome. Prompt ophthalmological evaluation is

needed in cases of traumatic brain injury or intracranial aneurysm ruptures, to prevent delay in diagnosis of the disease.

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This paper was judged as the BEST PAPER of Vitreo Retinal Diseases – III Session

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Consultant, Retina Work

Narayana Nethralaya

NOVEL GENOTYPE-PHENOTYPE CORRELATION AND EXPLORING POTENTIAL FOR GENE THERAPY IN STARGARDT DISEASE

Stargardt's disease, (STGD1) [MIM 248200] originally described by Dr. 'Karl Stargardt', is the most common inherited form of juvenile macular degeneration causing progressive bilateral vision loss that may end in legal blindness(1). Disease onset occurs between 6 to 12 years of age affecting 1 in 8000 to 10,000 individuals in the United States and remained untreatable till date sharing about 7% of all retinal degenerations(2,3). The exact prevalence of the disease in Asian countries, including India is not known due to the paucity of reports from the region.

Patients with Stargardt's experience a gradual deterioration of central vision while the peripheral vision is usually preserved. The gradual loss of central vision vision makes patient difficult to recognize faces, which may be accompanied with other problems such as photophobia, colour vision abnormalities, parafoveal scotomata, slow dark adaptation and night blindness (4, 5, 6). During the clinical examination, autofluorescence (AF) imaging can show areas of RPE atrophy, bull's-eye changes in the macula, flecks and peripapillary sparing.(7) The fluorescein angiography shows a

"dark-choroid" effect in many Stargardt patients due to blockage of background choroidal circulation by A2E accumulation, resulting in a finding that is variously known as a dark, silent, or masked choroid (8, 9). However, fluorescein angiography is not applied routinely in the workup of patients suspected of ABCA4 disease due to evidence that exposure to visible light is a cofactor in the disease. OCT can be used to study the extent of outer neural retinal loss and RPE atrophy (10,11). Electrophysiological studies through ERG in Stargardt patients reveal that they usually maintain normal or subnormal full-field scotopic (rods) and photopic (cones).

Stargardt's disease may be misdiagnosed due to genetic complexity and overlapping clinical phenotypes. To develop new therapeutic approaches and accurate genetic counselling of affected patients and their family members, it is important to know the detailed clinical diagnosis and genotype-phenotype correlations. Hence we studied a total of 35 families, where all probands and 84 family members were studied. Detailed medical history was obtained, followed by clinical examination including best-corrected Snellen visual acuity (BCVA), slit-lamp examination, Gonioscopy, indirect ophthalmoscopy and fundus photography. Fundus autofluorescence (FAF) imaging with a confocal scanning laser ophthalmoscope (Spectralis, Heidelberg Engineering, Heidelberg, Germany) in all patients and selected family members was performed. Spectral domain optical coherence tomography (SD OCT; Spectralis, Heidelberg Engineering, Heidelberg, Germany) was also performed simultaneously in most of these patients and in pediatric cases a handheld SD-OCT (Envisu 2300, Bioptigen, DNC, USA) was performed. Electrophysiologic examinations were conducted according to the standards given by the International Society of Clinical Electrophysiology in Vision. 18, 19 Viking 5.0 Ganzfeld dome (Nicolet Biomedical Instruments, Madison, Wisconsin, USA) with a light-emitting

diode for light stimulation was used for both electro-oculography and full-field electroretinography in selected patients and genetic analyses using whole exome sequencing was performed. Each family underwent a pedigree analysis to establish inheritance patterns and the genotype. The status of each identified mutations in affected as well as unaffected subjects under study was analyzed. Each of these identified mutations was checked for their segregation in the family. Carrier frequency based on the heterozygous state of individual was calculated. Pathogenic score for each identified changes were analyzed. Electrophysiological tests were carried out wherever required.

The prospective study was approved by the Institutional Review Board and was performed as per institutional ethics guidelines and in accordance with the tenets of the Declaration of Helsinki. Subjects were recruited for the study after obtaining informed written consent either from the patient or the guardian and family members.

Age at presentation varied between 11yrs to 64 years with mean age of 24yrs. A spectrum of fundus abnormalities were observed which included varying degree of fleck distribution, choroidal changes, mid peripheral changes and also overlapping features with other dystrophies. Clinical variations within the family with same mutation were also observed. Multiple novel mutations and rare inheritance patterns were detected in 8 families. Electrophysiological tests and mutations found to have prognostic significance. Majority of mutations were missense (n-35) followed by termination (n-12), splice site (n-10) and frameshift (n-2). N mutations were reported first time in this study. The status of these identified mutations were analyzed in the family members.

Stargardt's disease can present with various phenotypic variations with complex genotype. Early detection may help to take measures to prevent

progression to an extent. Our study also adds a good data base for future prospects of gene therapy and drug trials.

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This paper was judged as the BEST PAPER of Vitreo Retinal Diseases – IV Session

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CLINICAL EVALUATION OF A NOVEL CRISPR/CAS12A BASED DIAGNOSTIC TOOL FOR FUNGAL ENDOPHTHALMITIS

INTRODUCTION:

Fungal diseases are estimated to be responsible for more than 1.6 million deaths annually and over 1 billion people suffer from fungal infections worldwide. Despite the substantial morbidity and mortality associated with fungal infections, they remain an underestimated and neglected global public health problem. Though pathogenic fungi can infect various organ systems of the human body, fungal infections of the eye are particularly devastating for several reasons. Keratitis and endophthalmitis are the common ocular fungal infections and even in best case scenarios, the visual rehabilitation and long-term visual outcomes are not optimal in these conditions. Expedient initiation of treatment drastically improves the clinical outcomes with time to diagnosis being one of the most important risk factors influencing morbidity and mortality in ocular and systemic fungal infections. However, conventional mycological diagnostic modalities require expertise and are often time consuming.

The rapidity, superior sensitivity and specificity of molecular methods for fungal DNA detection, such as Polymerase Chain Reaction (PCR), have been

reported both with ocular and systemic fungal infections. Nucleic acid detection techniques are especially advantageous in fungal keratitis (FK) where the empirical use of antimicrobial therapy and in fungal endophthalmitis (FE) where the low yield from clinical samples decreases the sensitivity of conventional mycological diagnostic techniques. However, PCR remains a high-complexity technique requiring expensive equipment and trained personnel precluding its use in resource limited settings.

Microbial clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated (CRISPR-Cas) adaptive immune systems contain programmable endonucleases with distinctive enzymatic properties that can be leveraged for the detection of microbial nucleic acids. Recent studies have highlighted the potential of these CRISPR-based nucleic acid detection methods as rapid and highly sensitive diagnostic modalities to detect pathogenic bacteria and viruses. However, the utility of these CRISPR-based diagnostic methods to diagnose fungal infections and their role as a potential diagnostic platform for ophthalmic infections remains to be elucidated.

Here, we describe the development of a rapid, ultrasensitive easy-to-implement CRISPR–Cas12-based tool, Rapid Identification of Mycoses using CRISPR (RID-MyC), for the detection of fungal nucleic acids. We have also validated our method using contrived reference samples and clinical samples from patients with suspected infective endophthalmitis.

PATIENTS AND METHODS:

RPA primer and gRNA screening

Small-subunit (18S) rRNA gene sequences from 49 relevant fungal species were accessed via the GenBank database and were aligned by using CLUSTAL Omega. Conserved sequences were identified to generate target

recombinase polymerase amplification (RPA) primers and CRISPR guide RNA (gRNA) sequences. The specificity of the designed RPA primers and gRNA sequences were tested using the PRIMER-Blast Program. The RPA primers were constructed as per manufacturer's instructions and the gRNA sequences were designed within the RPA amplicons based upon protospacer adjacent motif (PAM) recognized by Cas12a.

OPTIMIZATION OF THE RID-MYC ASSAY

The RID-MyC diagnostic platform combines RPA and CRISPR/Cas12a detection. The RPA reaction was performed as per the manufacturer's instructions (TwistAmp Basic, TwistDx, Cambridge, United Kingdom). The 50-µl reaction mixture containing 0.48 µM forward and reverse primers, 29.5 µl primer free rehydration buffer, 5 µl template DNA, and 14 mM magnesium acetate (MgOAc) was incubated at 39°C for 30 minutes. LbCas12a trans-cleavage assays were performed similarly to those previously described. Briefly, a total of 50 nM LbCas12a (New England Biolabs Inc., Ipswich, MA USA) was preincubated with 500 nM CrRNA gRNA in 1× NEBuffer 2.1 for 10 min at 25 °C. After formation of the RNA–protein complex, 12 µl of the RPA amplicon and 1 µM of a quenched fluorescent ssDNA reporter were added and incubated at 37°C for 30 min or the denoted time in figures. For fluorescence detection, a ssDNA reporter with a 5′ end-labelled FAM group and a 3′ end attached to an Black quencher (/56-FAM/TTATT/3BHQ/) was used. Real-time and endpoint fluorescence was the raw fluorescence determined by the Real-Time PCR Detection System. Visual detection was accomplished through imaging the tubes in the LED blue light illuminator and the Bio-Rad ChemiDoc MP Imaging System (Bio-Rad., Hercules, CA USA) with its built-in UV channel.

Determination of the Specificity and Analytical Sensitivity of the RID-MyC Assay

To determine the specificity and sensitivity of the RPA primers and the RID-MyC, the DNA extracted from cultures of the following organisms isolated from patients with FK was used: Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Fusarium oxysporum, Candida albicans, Lasiodiplodia theobromae, Alternaria alternata, Bipolaris, Curvularia, Exserohilum, Pseudomonas aeruginosa, Streptococcus pneumoniae, Staphylococcus aureus and Escherichia coli. To determine the sensitivity of the RPA primers, the RPA reactions were performed as described above and the amplified products were investigated using 2% agarose gel electrophoresis (AGE) (Figure 1). Real-time and endpoint fluorescence detection was used to determine the specificity of the RID-MyC assay using 50 ng DNA of the above listed isolates. The analytical limit of detection (LOD) was evaluated by testing the calibration standards of the following fungal species: *Aspergillus flavus*, *Candida albicans*, *Curvularia* and *Fusarium oxysporum*, prepared by serial dilutions at the following concentrations: 165 fM (10^5 copies), 16 fM (10^4 copies), 1.6 fM (10^3 copies), 165 zM (10^2 copies), 16 zM (10 copies) and 1.6 zM (1 copy).4

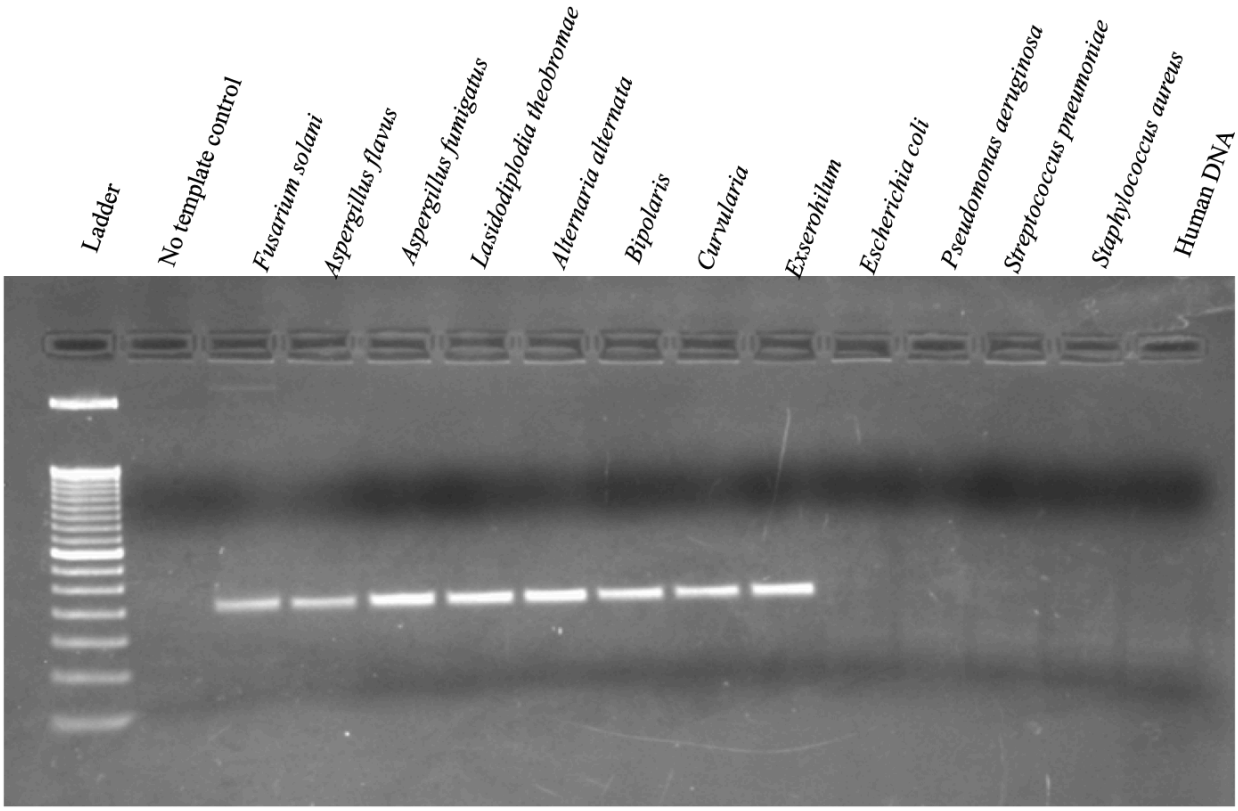

Figure 1: Agarose gel electrophoresis to demonstrate the specificity of the RPA primers

RID-MYC AND PCR IN CLINICAL SPECIMENS

Ninety-one intraocular specimens (Aqueous humor (AH), 24 and Vitreous fluid (VF), 57) from 68 consecutive patients with clinically suspected infective endophthalmitis and 10 control patients (VF, 10) undergoing vitrectomy for diabetic retinopathy presenting to our tertiary eye care facility were obtained as previously described. Informed consent was obtained from all participants, and the trial conformed to the Declaration of Helsinki. Ethical approval was obtained from the Aravind Eye Care System Institutional Review Board. DNA was isolated from the clinical specimens using the QIAmp DNA Mini kit and stored at -20°C until further use. The RID-MyC assay on the clinical specimens was performed as described above. Figure 2 illustrates the workflow of the RID-MyC assay for clinical specimens.

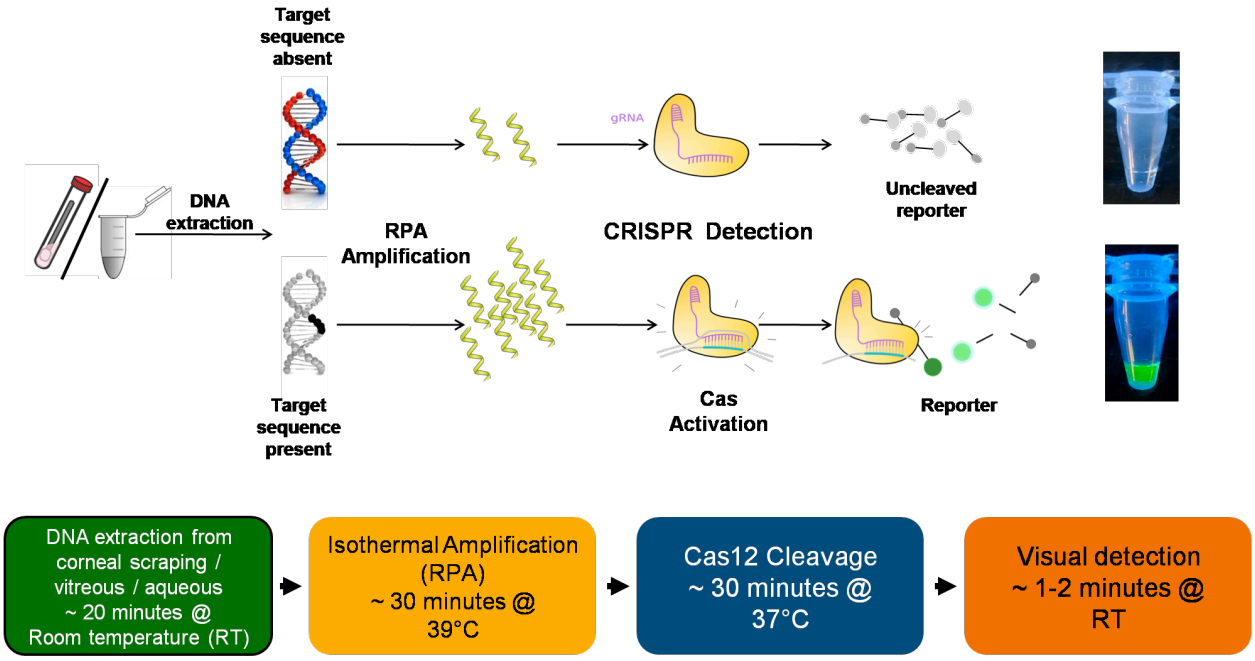

Figure 2: Schematic workflow of the RID-MyC Assay

CONVENTIONAL MICROBIOLOGIC INVESTIGATIONS

Immediately after collection, the intraocular specimens (AH and VF) from both the control and experimental groups were divided into 2 aliquots. One aliquot was sent for microbiological identification with Gram stain and culture by inoculation on blood agar, chocolate agar, thioglycolate broth, brain heart infusion broth, and potato dextrose agar within 30 minutes of collection. The remaining aliquot was immediately transferred aseptically into a presterilized microfuge tube and stored at -20°C for DNA extraction. Fungal smears were considered positive when fungal elements were seen under low-power magnification and reduced light. Fungal cultures were considered positive with growth on any 2 media or moderate to heavy growth on 1 medium. Both real-time and endpoint fluorescence detection was performed for all clinical samples. For the analysis of clinical samples, a RID-MyC assay result was considered positive if it was equal or greater than a cut-off threshold equal to the mean signal of the negative control samples

plus three times its standard deviation. PCR was performed as previously described and the amplified product was visualized on an ultraviolet transilluminator using 2% AGE incorporating 0.5 mg/ml ethidium bromide. Previously described panfungal primers [Forward primer sequence, 5′- GTG AAA TTG TTG AAA GGG AA -3′; and reverse primer sequence, 5′-GAC TCC TTG GTC CGT GTT -3] specific for the 28S rRNA gene were used in our study.

DISCREPANT ANALYSIS

For an intraocular specimen that demonstrated positive results for fungus by the RID-MyC assay but negative results by culture, the PCR product was sequenced to confirm the presence of fungal DNA in the sample. The amplified fragment was sequenced and the determined sequence was used to search for homologous sequences in GenBank using the BLASTN program (http://blast.ncbi.nlm.nih.gov) A sample was considered to be positive for fungus if it demonstrated positive results by culture or Gram stain. In addition, a sample also was considered to show positive results for fungus if positive results from sequencing were obtained or clinical course review (clinical findings and response to antifungals) also supported the presence of fungus in the corresponding eye.

STATISTICAL ANALYSIS

Background-subtracted fluorescence was calculated by subtraction of the fluorescence of no-template (water only as “template” input into the RID-MyC reaction) control wells on the plate from target fluorescence values evaluated in the assay run at the same time points in the assay. Statistical significances were analyzed by using Prism 8 (GraphPad Software, version 8.0.1). Student’s t tests were used for comparison of background-subtracted fluorescence. A P value of < 0.05 was considered statistically significant.

RESULTS:

Specificity and Analytical Sensitivity of the RID-MyC Assay

The specificity of the RID-MyC assay determined using DNA isolated from patient isolates demonstrated detection of Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Fusarium oxysporum, Candida albicans, Lasiodiplodia theobromae, Alternaria alternata, Bipolaris, Curvularia, and Exserohilum and no detection of Pseudomonas aeruginosa, Streptococcus pneumoniae, Staphylococcus aureus, Escherichia coli and human DNA, confirming high specificity (Figures 3). The analytical sensitivity of the RID-MyC assay was determined and the limit of detection (LoD) was 13.8 genomic copies for Aspergillus flavus (Figure 4), 16.6 for Fusarium solani (Figure 5), 13.9 for Curvularia lunata (Figure 6), and 13.3 for Candida albicans (Figure 7).

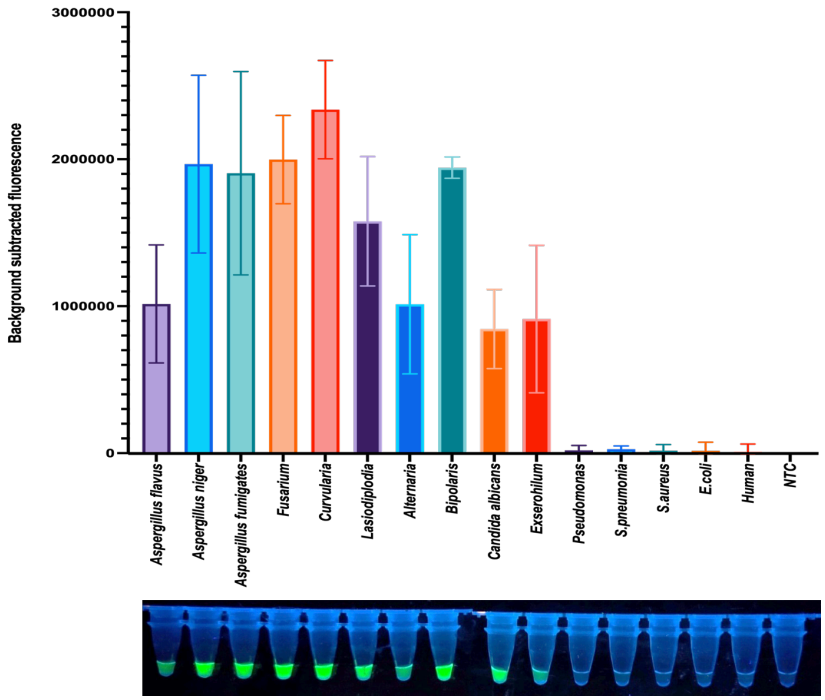

Figure 3: Specificity of real-time RID-MyC assay for detection of fungal nucleic acids

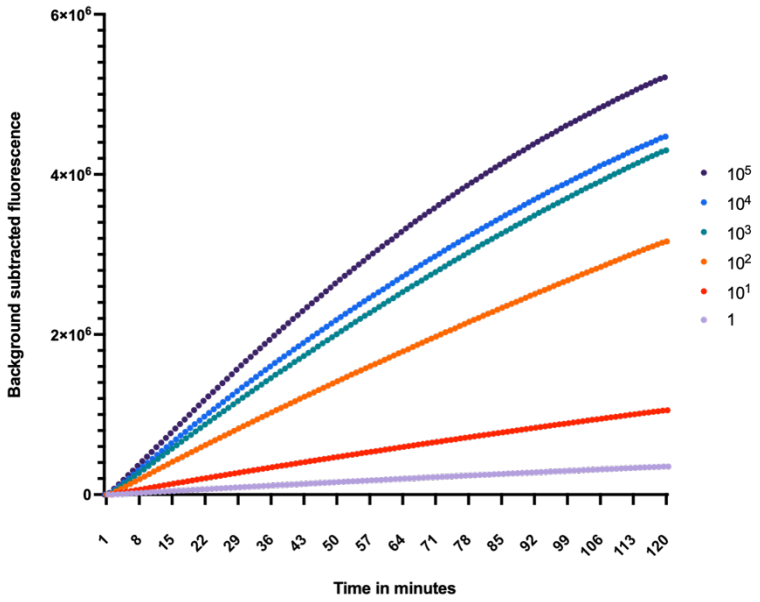

Figure 4: Real-time fluorescence kinetics of amplified Aspergillus flavus DNA gene fragments from 105–1 copies per µl

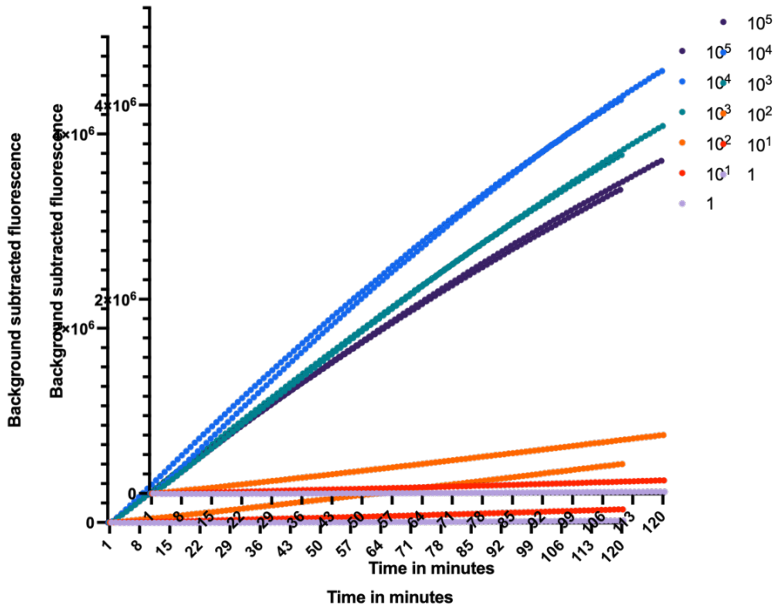

Figure 5: Real-time fluorescence kinetics of amplified Fusarium solani DNA gene fragments from 105–1 copies per µl

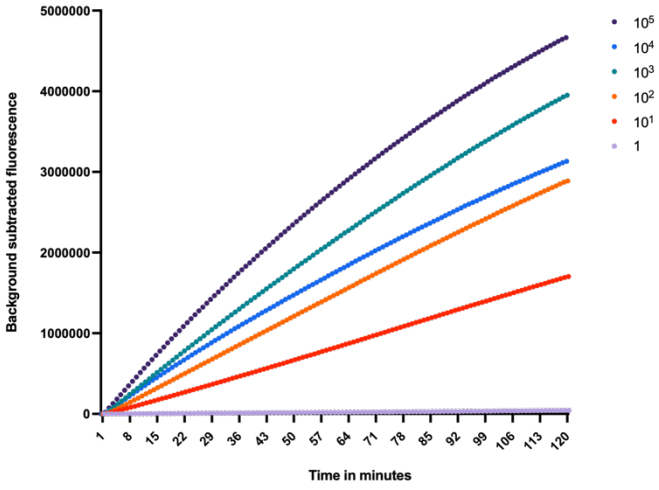

Figure 5: Real-time fluorescence kinetics of amplified Curvularia lunata DNA gene fragments from 105–1 copies per µl

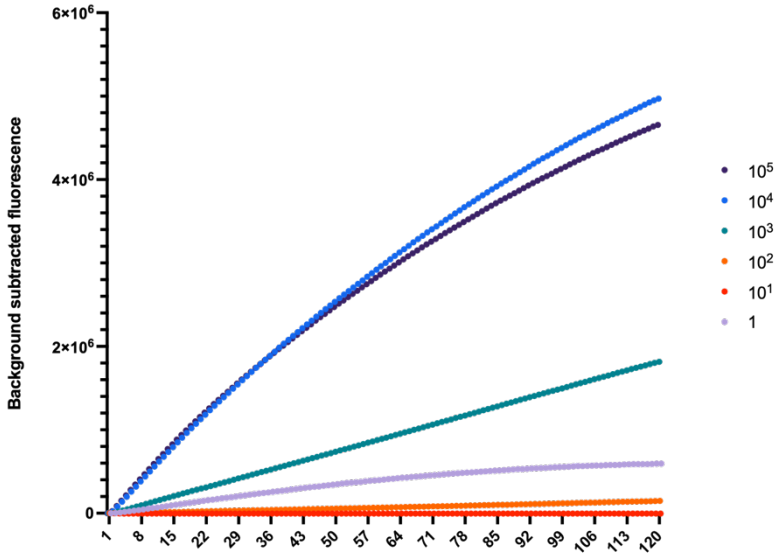

Figure 6: Real-time fluorescence kinetics of amplified Candida albicans DNA gene fragments from 105–1 copies per µl

Clinical performance of the RID-MyC assay in endophthalmitis

The results of the RID-MyC assay in correlation with culture and PCR for patients with suspected infective endophthalmitis are shown in Table 1. Of the 10 VF samples collected from control patients, none were positive for fungus by culture, PCR or RID-MyC. Among the 81 intraocular specimens collected from 68 patients, none were positive for fungus by conventional mycological examinations. Fifteen were positive for fungus by RID-MyC of which 13 were positive for fungus by panfungal PCR. Two samples were positive only by RID-MyC and not by PCR. To verify the presence of fungi in the discordant samples, the amplified region encompassing the 18S rRNA gene from each sample was sequenced, and the resulting sequences were used to search for homologous sequences in GenBank. The clinical course review and sequencing indicated that both discordant samples (RID-MyC positive but PCR negative) were from patients with fungal endophthalmitis. The concordance rate between PCR and RID-MyC was 95%.

CONCLUSION:

Here, we combined isothermal amplification and CRISPR-Cas12a to develop a rapid (45 – 60 min) and accurate assay for the diagnosis of fungal endophthalmitis. This is the first study to describe a CRISPR based assay for the broad range detection of fungal nucleic acid in any organ system and also the first study to describe a CRISPR based assay for the diagnosis of ophthalmic infections. The limitations of conventional mycological methods for the diagnosis of endophthalmitis has been previously established. Even nucleic acid detection strategies like PCR are susceptible to the intrinsic PCR inhibitors present in vitreous and aqueous samples. Recombinase polymerase amplification (RPA) has been previously shown to resistant to PCR inhibitors. The rapidity, superior sensitivity, specificity and cost-effectiveness of the CRISPR based RID-MyC assay makes it a valuable

addition to the diagnostic armamentarium for the diagnosis of fungal endophthalmitis.

Table 1: Results of Culture, PCR, RID-MyC Assay in intraocular specimens with suspected endophthalmitis

S. No	Specimen	Culture	RIDMyC	PCR
Endogenous Endophthalmitis				
1	Vitreous fluid	No growth	+	+
2	Vitreous fluid	No growth	-	-
3	Vitreous fluid	No growth	-	-
4	Aqueous humor	No growth	-	-
5	Aqueous humor	Nocardia spp.	-	-
6	Vitreous fluid	No growth	-	-
7	Vitreous fluid	No growth	-	-
8	Vitreous fluid	S.aureus	-	-
9	Vitreous fluid	No growth	-	-
10	Vitreous fluid	S.aureus	-	-
11	Vitreous fluid	No growth	-	-
12	Vitreous fluid	No growth	-	-
13	Vitreous fluid	No growth	-	-
14	Vitreous fluid	No growth	+	+
15	Vitreous fluid	No growth	-	-
16	Vitreous fluid	S.aureus	-	-
17	Aqueous humor	No growth	-	-
18	Aqueous humor	No growth	-	-
19	Vitreous fluid	No growth	+	+
20	Aqueous humor	No growth	-	-
21	Vitreous fluid	No growth	-	-

22	Aqueous humor	No growth	-	-
Postoperative Endophthalmitis				
23	Aqueous humor	No growth	-	-
24	Vitreous fluid	No growth	-	-
25	Vitreous fluid	No growth	-	-
26	Aqueous humor	No growth	-	-
27	Vitreous fluid	No growth	+	+
28	Aqueous humor	No growth	-	-
29	Vitreous fluid	No growth	-	-
30	Aqueous humor	No growth	-	-
31	Vitreous fluid	No growth	-	-
32	Aqueous humor	No growth	-	-
33	Vitreous fluid	No growth	-	-
34	Vitreous fluid	Pseudomonas stutzeri	-	-
35	Vitreous fluid	No growth	-	-
36	Vitreous fluid	No growth	-	-
37	Vitreous fluid	No growth	-	-
38	Vitreous fluid	No growth	-	-
39	Vitreous fluid	No growth	-	-
40	Vitreous fluid	No growth	-	-
41	Vitreous fluid	No growth	-	-
42	Aqueous humor	No growth	-	-
43	Aqueous humor	No growth	-	-
44	Vitreous fluid	No growth	+	+
45	Aqueous humor	No growth	+	-
46	Aqueous humor	No growth	+	+

47	Vitreous fluid	No growth	-	+
48	Vitreous fluid	No growth	+	+
49	Vitreous fluid	S.pneumoniae	+	+
Traumatic Endophthalmitis				
50	Vitreous fluid	No growth	-	-
51	Vitreous fluid	No growth	-	-
52	Aqueous humor	No growth	+	-
53	Vitreous fluid	No growth	+	+
54	Vitreous fluid	No growth	-	-
55	Vitreous fluid	No growth	-	-
56	Vitreous fluid	GNB	-	-
57	Vitreous fluid	No growth	-	-
58	Vitreous fluid	Streptococcus viridans	-	-
59	Vitreous fluid	S.pneumonoiae	-	-
60	Vitreous fluid	No growth	-	-
61	Vitreous fluid	No growth	-	-
62	Vitreous fluid	No growth	-	-
63	Vitreous fluid	No growth	-	-
64	Vitreous fluid	Streptococcus viridans	-	-
65	Vitreous fluid	No growth	-	-
66	Vitreous fluid	CONS	-	-
67	Vitreous fluid	No growth	-	-
68	Aqueous humor	No growth	-	-
69	Vitreous fluid	S.aureus	-	+
70	Aqueous humor	S.aureus	+	+

71	Vitreous fluid	Streptococcus viridans	+	+
72	Vitreous fluid	No growth	-	-
73	Aqueous humor	No growth	-	-
74	Vitreous fluid	No growth, CONS	-	-
75	Vitreous fluid	No growth	-	-
76	Aqueous humor	No growth	+	+
77	Vitreous fluid	No growth	-	-
78	Aqueous humor	No growth	-	-
79	Aqueous humor	No growth	-	-
80	Aqueous humor	No growth	-	-
81	Aqueous humor	No growth	+	+