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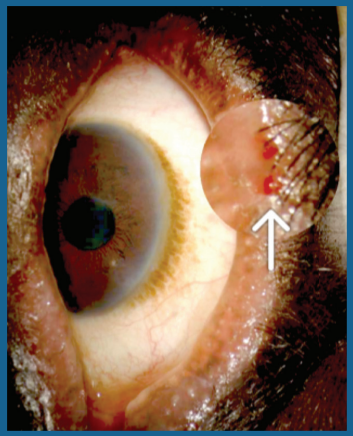

Ulcerative lesions at the lid margins

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Chief editor:
Paul Chew,
paul_chew@nuhs.edu.sg

Managing editor:
Keith Ong

Editorial office:
Asian Journal of Ophthalmology/
Kugler Publications,
P.O. Box 20538,
1001 NM Amsterdam,
The Netherlands.
info@asianjo.com

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Peer-review manager:
Kayoko Welsh,
Kayoko.Welsh@asianjo.com

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As new technologies and therapeutic interventions are continually being developed, Ophthalmology has become a field of rapid change, particularly in the Asia-Pacific region, where disease patterns and health care delivery differ greatly from those seen in the West. Asian Journal of Ophthalmology was established in 1998 with the aim of disseminating information relevant to Ophthalmology and glaucoma throughout Asia and to interested groups worldwide.

The objectives of Asian Journal of Ophthalmology are as follows:

- To provide a platform for the publication of information with a focus on Ophthalmology in Asia.
- To disseminate information that will improve the care of patients with all types of ophthalmological disorders, with a special focus on glaucoma.
- To increase the understanding of such disorders through reporting of educational activities.
- To publish the results of research programmes to expand knowledge about the causes, prevention, and treatment of ophthalmological disorders.
- To work closely with Asian and international researchers to achieve these aims.
- To provide a forum for young and relatively inexperienced researchers to present their research results as Original Articles via an international platform.
- To maintain and promote relationships with any organization with similar goals.

Although the focus of Asian Journal of Ophthalmology mainly was on glaucoma with close ties to the South-East Asian Glaucoma Interest Group (SEAGIG) in the past, the journal now focuses on the entire spectrum of Ophthalmology. This resulted in collaboration with the Asia Pacific Ophthalmic Trauma Society (APOTS).

The Asian Journal of Ophthalmology and Kugler Publications have started to collaborate since mid 2012 on the publication of the journal. A new website has been launched (www.asianjo.com), which facilitates all aspects of the peer-review and publication process, from manuscript submission to publication.

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Asian J Ophthalmol. 2018;16:060-061

Prevalence of variation in predicted refraction between different intraocular lens formulae

Keith Ong[1,2], Linda Feng[3]
[1]Royal North Shore Hospital Department of Ophthalmology, University of Sydney, Sydney, Australia; [2]Dalcross Adventist Hospital, Sydney, Australia; [3]Nepean Hospital, Sydney, Australia

Abstract

Variations of 0.5 D in predicted refraction between the different intraocular lens (IOL) calculation formulae may occur in 19.4% cases. This has implications when reporting refractive surprise. It also shows that it is beneficial to consider more than one IOL formula when choosing IOL power for cataract surgery.

Selecting the intraocular lens (IOL) power for cataract surgery can be a dilemma when there is a variation in predicted refraction between the different IOL formulae for a particular power of IOL.

The amount of refractive surprise (RS) can vary depending on which IOL calculation formula is used when there is a variation in predicted refraction. A small study was done to evaluate the prevalence and extent of this variation.

Four intraocular lens calculation formulae were compared: SRK/T, Haigis, Holladay 1, and Holladay 2. Zeiss IOL Master 500 was used. The cohort consisted of 105 eyes of 64 patients who had cataract phacoemulsification and insertion of posterior chamber IOL (Alcon SN60WF) in the months of January to June 2015.

The incidence and amount of discrepancy in predicted refraction between the different IOL formulae and their respective refractive surprise were analysed. The degree of variation was stratified into three groups: < 0.25 D; 0.25 to 0.5 D; and > 0.5 D. A variation of < 0.25 D was found in 46.2% cases. In 34.4% of cases, the variation was between 0.25 to 0.5 D. A discrepancy of > 0.5 D in IOL formula calculation was found in 19.4% of cases.

Hence, 19.4% of cases in this cohort had a variation of > 0.5 D in predicted refraction between the different IOL formulae. These cases were found to have axial length, anterior chamber depth, or keratometer readings that were beyond average, as well as anterior chamber depth disproportionate to axial length.

Variations in predicted refraction between different IOL formulae would be significant if it were > 0.5 D, because this could contribute to refractive surprise. Refractive surprise in this study was the difference between actual refraction

Correspondence: Dr. Keith Ong, 2 Railway Avenue, Eastwood NSW 2122, Australia.
E-mail: keithong@optusnet.com.au

two months after cataract surgery compared to the predicted refraction by the IOL formulae for that particular IOL used. Analysing the postoperative refractive results in the > 0.5 D group, we found the IOL formula that gave the least refractive surprise was Haigis in 50% of cases, Holladay 2 in 25% of cases, Holladay 1 in 15% of cases, and SRK/T in 10% of cases. This indicates that it is beneficial to consider more than one IOL formula when choosing IOL power in these cases as it appears that a particular formula may be more suitable for a particular eye. Therefore, when reporting refractive surprise, one has to consider the IOL calculation formula that was used for a particular patient.

A way to minimise the impact of variation in refractive prediction on refractive surprise is to find the formula that results in the least refractive surprise in the first cataract operation and then use this formula for IOL calculation when the second eye is being operated.

Asian J Ophthalmol. 2018;16:062-063

Glaucoma and frequent flying

Keith Ong[1], Leonard Ong[2], Lillian Armellin[3]
[1]Department of Ophthalmology, Northern Clinical School, University of Sydney, Sydney, NSW, Australia; [2]Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW, Australia; [3]Prince of Wales Clinical School, University of New South Wales, Sydney, NSW, Australia

A 58-year-old male has advanced normal tension glaucoma. He has had bilateral cataract surgery and trabeculectomy. Despite good intraocular pressure (IOP) control at 10-12 mmHg bilaterally, visual field loss has progressed.

He travels frequently for work, weekly on domestic and monthly on international flights. To investigate whether decreased oxygen saturation could be a factor in his glaucoma progression, a Fingertip Pulse Oximeter was used to measure his oxygen saturation (SpO_2) during a flight and provide an indirect measurement of arterial oxygen saturations. At ground level (5 metres above sea level at Sydney Airport), SpO_2 was 96-99%, while during cruising altitude, SpO_2 varied from 93-95%. Occasionally, it fell below 93% when he was dozing.

The author (KO) evaluated the findings personally during an international 8-hour flight with a Fingertip Pulse Oximeter (MD300C2A, Medical Development International, Beijing, China). It was a Sydney-Singapore flight (Singapore Airlines Airbus A380) and according to the captain of the flight, cabin pressure was set to simulate atmospheric pressure at an altitude of 6850 ft (2088 m).

The author's SpO_2 was 96 to 99% at sea level, and ranged from 89 to 95% during flight, giving an oxygen desaturation of up to 7% during cruising altitude. Several other volunteers reported similar findings of SpO_2 above 95% at sea level and below 95% at cruising altitude. Humphreys[1] also found in their study of 84 passengers aged 1-78 years that mean SpO_2 at ground level was 97% and at cruising altitude 93%, with 54% of passengers having SpO_2 values of 94% or less at cruising altitude.

The author also measured IOP during flight with the iCare PRO tonometer (Icare Finland Oy, Vantaa, Finland). IOP was about 12 mmHg at sea level and 14-15 mmHg during cruising altitude.

IOP is the difference between the pressure in the eye and atmospheric pressure. This can be demonstrated when an eye drop bottle is opened at cruising altitude and the contents extrude out because the pressure in the container is higher than atmospheric pressure in the cabin. Similarly, IOP would be higher when

Correspondence: Keith Ong, 2 Railway Avenue, Eastwood, NSW 2122, Australia.
E-mail: keithong@optusnet.com.au

atmospheric pressure is lower, and rapidly re-equilibrates due to the flow of aqueous and blood in and out of the eye. Facility of outflow would be a measure of this ability to re-equilibrate, and Foulsham and Tatham reported that filtration surgery may be protective against IOP fluctuations associated with ascent to high altitude.[2]

In the literature, some researchers have reported a decrease[3] and some have reported an increase[4] in IOP at high altitude. Some have attributed IOP rise to changes in central corneal thickness, but the latter may actually be a transient effect due to relative elevation of IOP when ambient pressure is reduced.

In summary, this case report has found that oxygen saturation can decrease by as much as 7% from baseline during cruising altitude, and IOP may rise 2-3 mmHg at cruising altitude. This would not be significant on short flights for a healthy person. However, in a patient with advanced glaucoma travelling on long haul flights, prolonged mild desaturation may contribute to optic nerve ischaemia and glaucoma progression. Hypoxia may be exacerbated if the subject has sleep apnoea and falls asleep during flight, or has a lung pathology such as emphysema that causes suboptimal gas exchange.

This anecdotal information would warrant a bigger study. It would also be useful to evaluate whether using an additional glaucoma eye drop, such as timolol, brimonidine (Alphagan), or brinzolamide (Azopt) can help. Acetazolamide (Diamox) has been used to help mountain sickness by lowering blood pH to encourage hyperventilation, which in turns helps improve oxygen saturation. If there is no allergy, perhaps taking half or a quarter tablet of acetazolamide 250 mg may lower IOP and also improve blood oxygenation.

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Asian J Ophthalmol. 2018;16:064-078

Macular thickness in diabetic retinopathy without clinically significant macular edema: a prospective study

Krishna Rao, Ravi Chandra, Lavanya Rao, Shailaja S, Manali Hazarika

Department of Ophthalmology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India

Abstract

Aim: *To measure macular thickness by optical coherence tomography (OCT) in various grades of diabetic retinopathy with no clinically significant macular edema (CSME) and its comparison with non-diabetics.*

Design: *Prospective cross–sectional study.*

Methods: *Macular thickness was measured by OCT in 72 healthy volunteers (107 control eyes), 45 patients with mild and moderate non-proliferative diabetic retinopathy (NPDR) (78 eyes), and 37 patients with severe NPDR and proliferative diabetic retinopathy (PDR) (66 eyes). Patients with diabetic macular edema (DME) as assessed by stereoscopic evaluation or photographs were excluded. One-way ANOVA test to compare the mean thickness and Tukey's test for multiple comparison between groups were used.*

Results: *Central subfield thickness (CST) was 238.57 ± 25.077 µm, 251.22 ± 24.649 µm, and 270.45 ± 28.956 µm in the three groups respectively. As the severity of retinopathy increased, the macular thickness significantly increased ($p = < 0.001$) in all the nine zones on OCT. There was a significant increase in CST noted in all the grades of retinopathy when compared with non-diabetics ($p = 0.004$, $p = < 0.0001$). No significant difference in macular thickness was noted between genders, irrespective of their groups ($p = 0.72$), or between the three groups in all the nine zones ($p = 0.609$).*

Conclusion: *There is a significant increase in CST in all grades of retinopathy, as well as with increasing severity of retinopathy when compared to non-diabetics. This warrants the need to obtain OCT measurements even in patients with moderate NPDR without CSME to rule out subclinical DME.*

Keywords*: central subfield thickness, diabetic retinopathy, macular thickness, optical coherence tomography, subclinical diabetic macular edema*

Correspondence: Manali Hazarika, Department of Ophthalmology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, PIN-576104, Udupi, Karnataka State, India.
E-mail: dr.manalihazarika@gmail.com

Introduction

The most common cause of visual loss in patients suffering from diabetic retinopathy is macular edema. This is a preventable cause of blindness and treatments that reduce diabetic macular edema (DME) can improve or stabilize visual acuity. The Early Treatment Diabetic Retinopathy Study (ETDRS) has demonstrated that focal (direct/grid) laser photocoagulation can reduce moderate vision loss from DME by 50% or more.[1] Hence, the quantitative and objective assessment of macular thickness is important.

Macular edema is routinely detected clinically by fundus examination using a contact lens through a biomicroscope. However, this is dependent on observer skill, patient co-operation, degree of pupillary dilatation, amount of media opacity, and the pattern of retinal edema.[2] Therefore, optical coherence tomography (OCT) has emerged as the ideal imaging modality in the evaluation and management of DME.

On comparing OCT with contact lens biomicroscopy for the detection of macular edema, Brown *et al.*[2] found excellent agreement between the two for the absence or presence of foveal edema when OCT thickness was normal (≤ 200 μm) or increased (> 300 μm). However, the agreement was poor when foveal thickness was only mildly increased (201-300 μm). This meant that contact lens biomicroscopy is relatively insensitive for the detection of mild foveal thickening, apparent on OCT.

This thickening, which cannot be detected clinically, but is present on quantitative indices of the centre point obtained from OCT, is termed as subclinical DME. This finding is of increasing clinical importance because it may be a forerunner for the development of clinically significant macular edema (CSME)[3,4] and finally lead to irreversible visual loss. The management has to be altered in such patients, and a shorter follow-up may be recommended in order to attain a better visual outcome.

Thus, the objectives of our study included the following:

1. To examine the relationship of OCT measured macular thickness to retinopathy severity in patients with diabetes, but without clinically detectable macular edema and its comparison with non-diabetics.
2. To verify the need for a change in protocol for follow-up in patients with diabetic retinopathy without CSME based on OCT measurements.

Methods

This was a prospective cross–sectional comparative study performed over a period of two years. The inclusion criteria for the group of cases were:

1. Patients with type 2 diabetes, with all grades of diabetic retinopathy as per ETDRS classification.[5]

2. Absence of DME, where DME was defined as retinal thickening, assessed by stereoscopic evaluation of the fundus by slit-lamp biomicroscopy or assessment of photographs.[6]

The control group was age- and sex-matched to the cases and did not have diabetes. The exclusion criteria were all those conditions that may affect macular thickness, such as prior treatment for DME and/or diabetic retinopathy, age-related macular degeneration, macular hole, post-cataract surgery of < 4 weeks duration, central serous retinopathy, renal failure, drug-induced like HCQ, and an OCT scan signal strength ≤ 4/10.

Ethical Committee clearance from the institution was obtained.

The subjects were divided into three groups: Group 1 included controls, *i.e.*, subjects without diabetes; Group 2 included patients with mild and moderate non-proliferative diabetic retinopathy (NPDR); and Group 3 included patients with severe NPDR and proliferative diabetic retinopathy (PDR).

All subjects underwent the following examination: best-corrected visual acuity with Snellen's chart, slit-lamp biomicroscopy with a 90-diopter lens, indirect ophthalmoscopy, fundus photography, and OCT. The OCT scans were acquired by centring at the fovea through a dilated pupil by a single examiner who was masked to the diagnosis of the patients. OCT imaging was performed with the Spectral domain (SD); Cirrus HD-OCT; Model 4000; Software version 4.0.

Macular Cube 512 x 128 scan protocol was obtained where a 6 × 6 mm area on the retina was scanned with 128 horizontal lines, each consisting of 512 A-scans per line within a scan time of 2.4 seconds. Scans with a signal strength > 5 that exhibited correct delineation of the retinal layers as detected automatically by the software and were without image artefacts were accepted. Central subfield thickness (CST), quantitative measurements within the four inner subfields, four outer subfields, and macular volume were taken directly from the automated analysis. CST was defined as the circular area of diameter 1 mm centred around the centre point; 128 thickness measurements were made in this circular area.[7]

CST values of ≥ 320 µm for males and 305 µm for females was considered as the cut-off value in diagnosing DME.8 Subclinical DME was considered present if this thickness was found to be ≥ 225 and ≤ 299 µm, according to the definition of the Diabetic Retinopathy Clinical Research Network (DRCR.net).[4]

Statistical analysis

Results were expressed as mean ± standard deviation. One-way ANOVA was used to compare if there was a significant difference in mean thickness between the three groups. Multiple comparison between groups was performed using Tukey's post-hoc test. An independent samples T test was performed to compare the mean thickness between groups having diabetes of various durations. Two-way

ANOVA was used to compare the relationship of mean thickness between males and females in the groups and in each of the zones. A p value of < 0.05 was considered statistically significant.

Results

A total of 251 eyes from 154 patients were included in the study. Group 1 had 107 eyes from 72 patients, Group 2 had 78 eyes from 45 patients, and Group 3 had 66 eyes from 37 patients. Of the 251 eyes, a total of 154 (61.3%) were males and 97 (38.6%) were females. Group 1 had 56 (52%) males and 51 (48%) females, Group 2 had 49 (63%) males and 29 (37%) females, and Group 3 had 49 (74%) males and 17 (26%) females.

The mean age in Group 1 was found to be 54.37 years, while in Group 2 it was 59.81 years, and in Group 3 it was 56.67 years. The mean age of the males was 56.47 years and that of females was 56.97 years.

The mean and standard deviation of OCT measurements of the nine zones in the three groups is highlighted in Table 1.

The one-way ANOVA test compared the means of the three groups and found that, as the severity of retinopathy increased, the macular thickness significantly increased (p = < 0.001) in all the nine zones. Similarly, the mean cube volume measurements also showed that there was a significant increase (p = < 0.001) in mean cube volume as the severity of retinopathy increased.

Table 1. Analysis of the mean macular thickness in the three groups using the one-way ANOVA test

Subfield zones	Controls Mean ± SD [µm]	Mild and moderate NPDR Mean ± SD [µm]	Severe NPDR and PDR Mean ± SD [µm]	p
Central	238.57 ± 25.077	251.22 ± 24.649	270.45 ± 28.956	< 0.001
Innernasal	308.91 ± 17.163	317.55 ± 16.382	322.83 ± 19.266	< 0.001
Outernasal	281.78 ± 18.044	291.19 ± 19.177	301.64 ± 22.665	< 0.001
Innertemporal	300.24 ± 21.264	309.18 ± 19.435	317.15 ± 19.129	< 0.001
Outertemporal	259.77 ± 20.602	270.88 ± 21.378	282.68 ± 28.062	< 0.001
Innersuperior	305.89 ± 21.739	319.86 ± 19.819	321.71 ± 20.770	< 0.001
Outersuperior	270.86 ± 18.206	280.50 ± 16.206	294.32 ± 28.477	< 0.001
Innerinferior	306.38 ± 21.263	314.38 ± 17.254	320.53 ± 18.623	< 0.001
Outerinferior	258.96 ± 18.295	274.28 ± 19.962	276.92 ± 20.612	< 0.001
Cube volume	9.764 ± 0.5253	10.105 ± 0.4509	10.462 ± 0.5317	< 0.001

On comparing the mean macular thickness between Group 1 eyes with the other two groups, we found that there was a statistically significant difference in all the nine zones, as shown in Table 2. This meant that there was a significant increase in macular thickness in all grades of diabetic retinopathy when compared with non-diabetics. A similar significant increase in mean macular thickness was also noted as the severity of diabetic retinopathy increased. Table 2 shows the comparison between Groups 2 and 3, where it was seen that most of the zones showed a statistically significant difference in the mean macular thickness excepting the inner nasal, inner superior, inner inferior, and outer inferior zones.

Table 2. Inter group comparison of mean macular thickness using Tukey's post-hoc test

Subfield zones	Groups	P
Central	Mild-Moderate NPDR vs Controls	0.004
	Severe NPDR & PDR vs Controls	< 0.0001
	Mild-Moderate NPDR vs Severe NPDR & PDR	< 0.0001
Innernasal	Mild-Moderate NPDR vs Controls	0.003
	Severe NPDR & PDR vs Controls	< 0.0001
	Mild-Moderate NPDR vs Severe NPDR & PDR	0.17
Outernasal	Mild-Moderate NPDR vs Controls	0.004
	Severe NPDR & PDR vs Controls	< 0.0001
	Mild-Moderate NPDR vs Severe NPDR & PDR	0.003
Innertemporal	Mild-Moderate NPDR vs Controls	0.006
	Severe NPDR and PDR vs Controls	< 0.0001
	Mild-Moderate NPDR vs Severe NPDR & PDR	0.049
Outertemporal	Mild-Moderate NPDR vs Controls	0.004
	Severe NPDR & PDR vs Controls	< 0.0001
	Mild-Moderate NPDR vs Severe NPDR & PDR	0.007
Innersuperior	Mild-Moderate NPDR vs Controls	< 0.0001
	SevereNPDR & PDR vs Controls	< 0.0001
	Mild-Moderate NPDR vs Severe NPDR & PDR	0.857
Outersuperior	Mild-Moderate NPDR vs Controls	0.004
	Severe NPDR and PDR vs Controls	< 0.0001
	Mild-Moderate NPDR vs Severe NPDR & PDR	< 0.0001

Subfield zones	Groups	P
Innerinferior	Mild-Moderate NPDR vs Controls	0.017
	Severe NPDR and PDR vs Controls	< 0.0001
	Mild-Moderate NPDR vs Severe NPDR & PDR	0.143
Outerinferior	Mild-Moderate NPDR vs Controls	< 0.0001
	Severe NPDR & PDR vs Controls	< 0.0001
	Mild-Moderate NPDR vs Severe NPDR & PDR	0.696

Table 3 and Figure 1 show the analysis of mean macular thickness when sorted by gender. In all the zones, there was no statistically significant difference between male and female eyes when compared, irrespective of their groups ($p = 0.720$). Likewise, the two-way ANOVA test, which was used to compare the thickness between the two genders in the three groups and in all the zones, did not find any statistically significant difference ($p = 0.609$).

An independent samples T test was performed to compare the mean macular thickness in relation to the duration of diabetes. In Group 2, there were 67 patients with diabetes of < 5 years duration and 11 patients with > 5 years duration. Table 4 and Figure 2 show that no statistically significant difference was found in the mean macular thickness in this group in any of the zones, although the mean macular thickness in most of the zones except in the outer temporal, inner superior, and outer superior zones was found to be higher in patients with > 5 years duration of diabetes.

Table 5 and Figure 3 highlight the mean macular thickness in relation to the duration of diabetes in Group 3. There were 52 patients with diabetes of < 5 years duration and 14 patients with > 5 years duration. The mean macular thickness in four zones, *i.e.*, the central, outer nasal, outer temporal, and outer superior zones, was higher in patients with diabetes of > 5 years duration. However, it was not statistically significant in any zone excepting the inner temporal zone.

Table 6 and Figure 4 show the comparison of the mean macular thickness in relation to a longer duration of diabetes. In Group 2, there were 75 patients with diabetes of < 10 years duration and 3 patients with > 10 years duration. The thickness in all nine zones was higher in patients with > 10 years duration of diabetes. However, it was statistically significant in only three zones, *i.e.*, inner nasal, outer nasal, and outer inferior.

Table 7 and Figure 5 show that in Group 3, consisting of 58 patients with diabetes of < 10 years duration and 8 patients with > 10 years duration, the mean macular thickness in eight zones, except in the inner temporal zone, was higher in patients with >10 years duration of diabetes, but not statistically significant in any zone.

Table 3. Analysis of the mean macular thickness sorted by gender

Subfield zones	Males Mean ± SD [µm]	Females Mean ± SD [µm]
Central	252.21 ± 30.50	248.77 ± 26.31
Innernasal	316.25 ± 19.22	313.68 ± 16.96
Outernasal	292.49 ± 21.51	285.85 ± 20.19
Innertemporal	309.14 ± 21.25	304.81 ± 21.06
Outertemporal	271.47 ± 25.96	265.71 ± 22.37
Innersuperior	314.79 ± 20.87	313.75 ± 24.00
Outersuperior	282.75 ± 24.63	275.70 ± 19.04
Innerinferior	314.35 ± 20.90	309.79 ± 18.78
Outerinferior	268.50 ± 22.86	268.36 ± 17.94
Cube volume	10.079 ± 0.602	10.013 ± 0.538

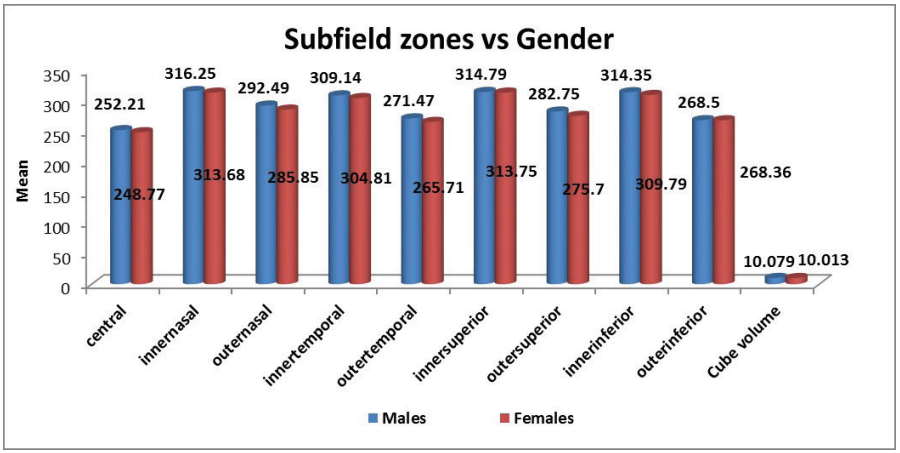


Table 4. Comparison of mean macular thickness in relation to the duration of diabetes in Group 2 (< 5 years vs > 5 years)

Subfield zones	Diabetes duration	Mean ± SD	p
Central	1	251.21 ± 24.93	0.994
	2	251.27 ± 23.99	
Innernasal	1	316.12 ± 15.89	0.56
	2	326.27 ± 17.38	
Outernasal	1	290.12 ± 19.24	0.225
	2	297.73 ± 18.29	
Innertemporal	1	308.84 ± 19.93	0.703
	2	311.27 ± 16.76	
Outertemporal	1	272.19 ± 21.98	0.184
	2	262.91 ± 15.75	
Innersuperior	1	319.90 ± 20.34	0.968
	2	319.64 ± 17.13	
Outersuperior	1	281.93 ± 16.18	0.55
	2	271.82 ± 14.06	
Innerinferior	1	313.73 ± 16.85	0.413
	2	318.36 ± 19.93	
Outerinferior	1	274.27 ± 19.65	0.988
	2	274.36 ± 22.77	

Duration of diabetes: 1 = < 5 years duration; 2 = > 5 years duration

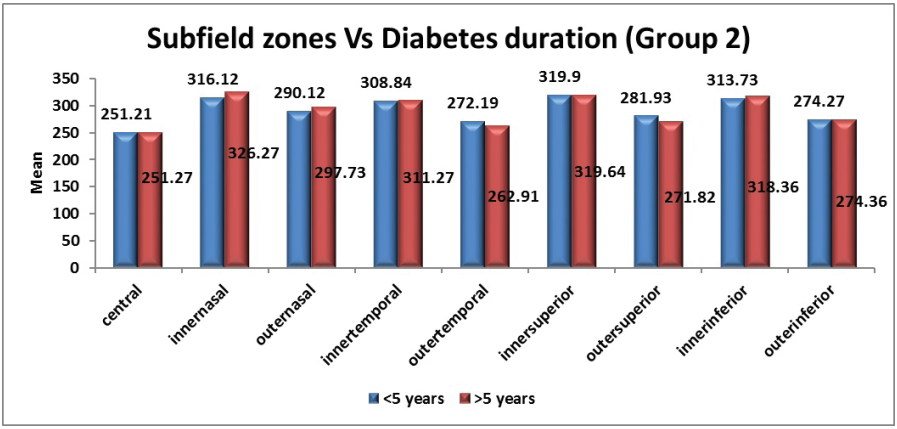


Table 5. Comparison of mean macular thickness in relation to the duration of diabetes in Group 3 (< 5 years vs > 5 years)

Subfield zones	Diabetes duration	Mean ± SD	P
Central	1	269.96 ± 28.94	0.792
	2	272.29 ± 30.04	
Innernasal	1	323.87 ± 16.67	0.534
	2	319.00 ± 27.32	
Outernasal	1	301.37 ± 23.28	0.853
	2	302.64 ± 20.10	
Innertemporal	1	320.23 ± 14.12	0.011
	2	305.71 ± 29.50	
Outertemporal	1	282.46 ± 29.14	0.903
	2	283.50 ± 24.67	
Innersuperior	1	322.21 ± 18.19	0.778
	2	319.86 ± 29.24	
Outersuperior	1	293.06 ± 29.69	0.493
	2	299.00 ± 23.78	
Innerinferior	1	321.48 ± 16.02	0.428
	2	317.00 ± 26.64	
Outerinferior	1	277.46 ± 21.11	0.686
	2	274.93 ± 19.26	

Duration of diabetes: 1 = < 5 years duration; 2 = > 5 years duration

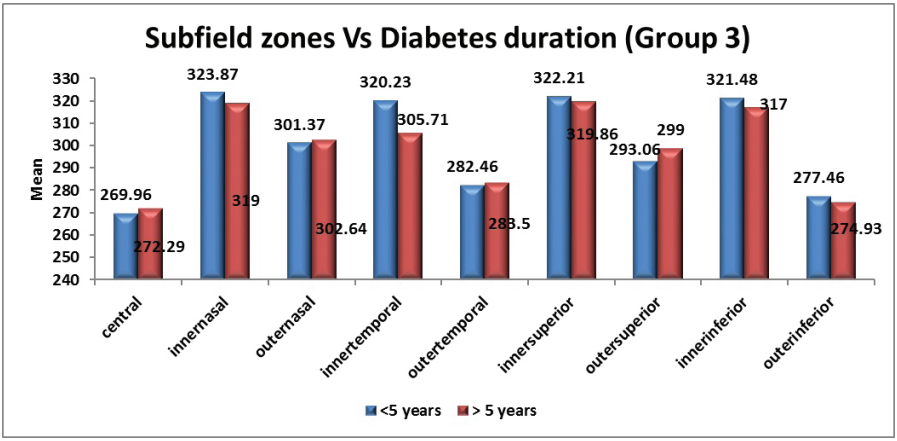


Table 6. Comparison of mean macular thickness in relation to the duration of diabetes in Group 2 (< 10 years vs > 10 years)

Subfield zones	Diabetes duration	Mean ± SD	P
Central	1	316.75 ± 16.04	0.029
	3	337.67 ± 13.61	
Innernasal	1	290.15 ± 18.48	0.015
	3	317.33 ± 21.22	
Outernasal	1	308.40 ± 19.26	0.076
	3	328.67 ± 14.98	
Innertemporal	1	270.45 ± 21.67	0.376
	3	281.67 ± 6.66	
Outertemporal	1	319.03 ± 19.62	0.063
	3	340.67 ± 14.50	
Innersuperior	1	280.17 ± 16.40	0.377
	3	288.67 ± 7.57	
Outersuperior	1	314.15 ± 16.81	0.546
	3	320.33 ± 30.90	
Innerinferior	1	273.20 ± 19.11	0.016
	3	301.33 ± 26.10	

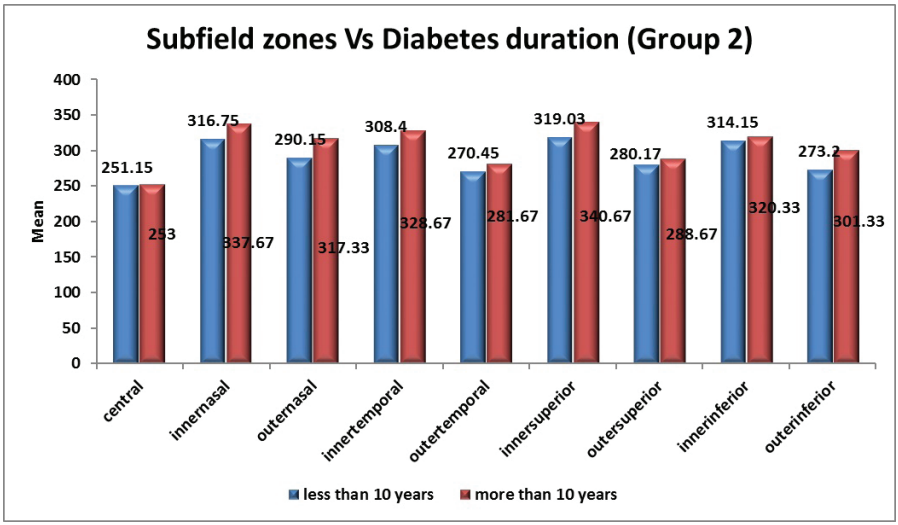


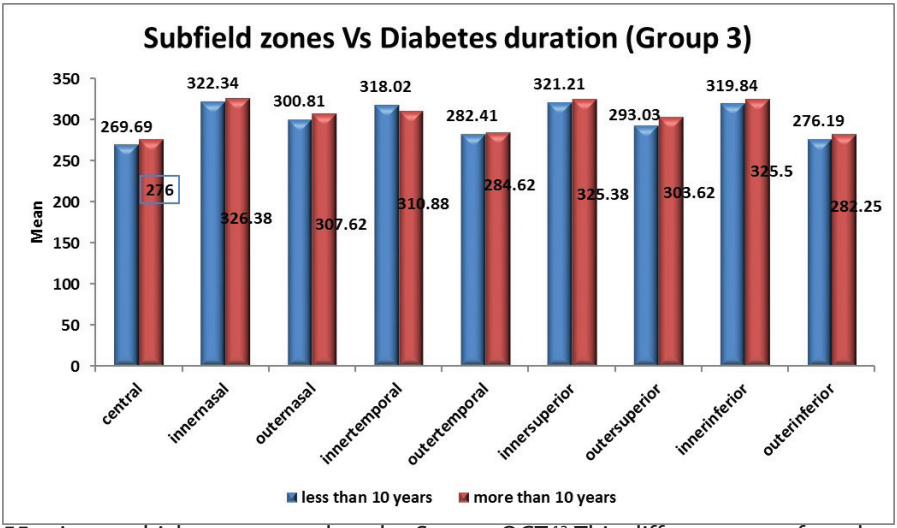
Table 7. Comparison of mean macular thickness in relation to the duration of diabetes in Group 3 (< 10 years vs > 10 years)

Subfield zones	Diabetes duration	Mean ± SD	P
Central	1	269.69 ± 28.52	0.567
	3	276.00 ± 33.53	
Innernasal	1	322.34 ± 18.03	0.583
	3	326.38 ± 27.97	
Outernasal	1	300.81 ± 22.57	0.430
	3	307.62 ± 23.96	
Innertemporal	1	318.02 ± 18.58	0.326
	3	310.88 ± 23.17	
Outertemporal	1	282.41 ± 28.80	0.836
	3	284.62 ± 23.51	
Innersuperior	1	321.21 ± 19.72	0.599
	3	325.38 ± 28.64	
Outersuperior	1	293.03 ± 29.53	0.328
	3	303.62 ± 17.78	
Innerinferior	1	319.84 ± 17.89	0.425
	3	325.50 ± 24.13	
Outerinferior	1	276.19 ± 21.26	0.440
	3	282.25 ± 15.06	

Duration of diabetes: 1 = < 10 years duration; 3 = > 10 years duration

Discussion

The DRCR.net had primarily used the TD-OCT in its studies related to measurements of DME up until 2011.[9] They have established a mean CST of 250 µm as the cut-off value to represent the upper limit of normal macular thickness. However, with the advent of Fourier domain (SD) OCTs, most studies have started using these devices due to better resolution. With the Spectralis SD-OCT, Grover *et al.*[10] found the mean CST in normal eyes to be 270.2 ± 22.5 µm. In contrast, the corresponding values on the TD-OCT (Stratus) were 212 ± 20 µm. Jean-Antoine *et al.*[11] noted a 50 µm increase in CST in favour of the Cirrus OCT as compared to the Stratus OCT. Similarly, other studies that have compared data obtained using the Stratus OCT and the Cirrus HD-OCT in both normals and patients with DME, have demonstrated that the median difference between Stratus and Cirrus CST was 43 µm,[9] *i.e.*, that Cirrus OCT measured retinal thickening was between 30 to



55 microns thicker compared to the Stratus OCT.[12] This difference was found to be based on the fact that the boundaries of the retina used to demarcate the macular thickness in TD-OCT are the internal limiting membrane and the junction between the inner and outer segments of the photoreceptors as opposed to the SD-OCT, which measures the distance between the retinal pigment epithelium and the inner limiting membrane. Thus, Grover *et al.*[10] have proposed 315 µm as the upper limit and 225 µm as the lower limit of normal CST.

Appukuttan *et al.*[13] have suggested a lower range, *i.e.*, 220-300 µm, be taken as the normal for central foveal thickness in Indian eyes using SD-OCT, with men having a greater central foveal thickness than women.

The major hurdle in our study has been to integrate the data from the Stratus OCT, used in our reference studies, into the Cirrus OCT, used in our study, so as to formulate normative values that will enable our measurements to be both accurately assessed and clinically applicable.

Taking the aforementioned normative values into consideration, our study found that there was a significant increase in macular thickness in all grades of retinopathy when compared with non-diabetics. When non-diabetic eyes were compared with eyes of mild and moderate NPDR, the highest increase in mean macular thickness was noted in the parafoveal zones followed by the central zone, but when such a comparison was done with eyes of more severe grades of retinopathy, the highest increase was in the CST. This phenomenon may probably be due to fluid leaking from retinal vessels into the parafoveal zones, with relative sparing of the foveal region in milder grades of retinopathy as well as due to the breakdown of the outer blood retinal barrier affecting the Müller cells that are

more abundant in the foveal floor than in the retinal edges14 in severe grades of diabetic retinopathy.

In contrast, Goebel *et al.*[15], in their study of diabetic patients of unspecified grade of retinopathy without CSME and unspecified gender, found that foveal and average retinal thickness did not differ from normal eyes. This could be because they pooled both genders and all grades of retinopathy, unlike our study.

In a study similar to ours, Browning *et al.*[16] had stratified the eyes of patients with diabetes based on gender and retinopathy severity, finding that there was a significant difference between the CST in the normal and the severe NPDR/PDR groups, as well as between the mild/moderate NPDR vs severe NPDR/PDR groups. The mean thicknesses of paracentral subfields did not show differences for normals or for any group.

In both females and males, they found a significant difference between CST in the severe NPDR/PDR groups, but no significant differences in other pairwise comparisons by retinopathy severity. Our study, however, did not find any statistically significant difference in the mean macular thickness between male and female eyes in any of the nine zones nor across the three groups compared. The importance of gender differences in macular thickness is limited to comparisons of groups in clinical studies. There is no clinical significance, as management remains the same, irrespective of gender.

When duration of diabetes was taken into account, we found that although the mean macular thickness was greater in eyes with diabetes of > 5 years duration in most zones, it was statistically significant in only one zone. Similar results were found when a longer 10-year duration was taken into consideration. Likewise, Goebel *et al.*[15] did not find any association between retinal thickness and duration of diabetes. However, Browning *et al.*[16] found statistically significant differences in duration of diabetes among groups of diabetics and varying levels of retinopathy severity.

Sanchez-Tocino *et al.*[17] found significant differences in foveal thickness between eyes in the control group and eyes in all the other groups, which were similar to our study. However, contrary to our study, they did not find significant differences in thickness in any zone in eyes with NPDR without CSME and PDR without CSME. They suggested that a foveal thickness greater than 180 µm may be useful for the early detection of macular thickening. Hee *et al.*[18] found similar results and reported 216 µm as the maximum value observed in normal eyes. However, the shortcomings of these studies were the manual measurements of TD-OCT readings, lack of gender stratification, and inclusion of eyes with CSME.

The fact that eyes with CSME were excluded from our study means that, as the severity of retinopathy increases, subclinical DME becomes more prevalent, which is in concordance with the Browning *et al.*[16] study.

Bressler *et al.*[4] suggested that approximately one-quarter to one-half of eyes with subclinical DME will progress to more definite thickening or will need treatment for DME within two years of its identification. Progression to CSME has been found to occur over a median period of 14 months by Browning *et al.*[16] Therefore, earlier detection of subclinical DME is preferred with the aim of preserving photoreceptors at early disease stages and retaining central visual acuity.

At this juncture, the question arises: at what level of CST and of severity of diabetic retinopathy without CSME should we begin obtaining OCT scans? Although it would be ideal to perform the OCT scans at the mild NPDR level itself, it is not always financially and practically feasible to obtain an OCT for every such patient in the Indian scenario. Earlier and more frequent follow-up would be more beneficial in these cases.

Hence, we suggest that it is more useful to perform an OCT scan in all patients with moderate NPDR levels of retinopathy, even in the absence of CSME, in order to monitor for increased CST and allow timely intervention to be decided upon. A CST of 251.22 ± 24.65 μm could be considered the cut-off point.

However, the decision to treat cannot be based entirely on OCT values and should be individualized depending on the level of visual acuity, patient compliance, and systemic factors such as hypertension and renal disease.[19]

In conclusion, our study is the first to provide information relating to retinopathy severity and macular thickness as measured by SD-OCT in a large cross-section of Indian eyes without DME. Unlike previous studies, our study was a prospective one, employed gender stratification, and considered the duration of diabetes. Patients with moderate NPDR without CSME would benefit from OCT measurements at each visit, so that upon detection of subclinical DME, a decision to frequently follow-up or initiate treatment may be recommended, thus preventing the visual loss that would occur by pursuing a normal follow-up regimen.

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Influence of anterior chamber depth on postoperative refractive outcome in Chinese eyes

Rachel SH Wong[1], Keith Ong[2,3]
[1]Discipline of Clinical Ophthalmology & Eye Health, University of Sydney, Sydney, Australia; [2]Royal North Shore Hospital Department of Ophthalmology, University of Sydney, Sydney, Australia; [3]Dalcross Adventist Hospital, Sydney, Australia

Abstract

Aim or Purpose: *This study aims to evaluate the refractive surprise (RS) after cataract surgery with various intraocular lens (IOL) formulas in eyes with very shallow or deep anterior chamber depth (ACD).*

Design: *This is a prospective cohort study of patients from a private ophthalmology practice in Sydney.*

Methods: *Thirty-one patients who had their cataract surgery in 2014 were included. The cohort consists of 20 eyes with ACD < 2.8 mm and 25 eyes with ACD > 3.2 mm. Patients' demographic variables and their predicted refractive outcomes using the SRK-T, Haigis, Holladay 1, and Holladay 2 IOL formulas were collected. Actual refractive outcomes were obtained from consultations at least one-month postoperatively. RS was calculated from the difference between predicted refraction outcome of IOL formulas and the actual postoperative refraction achieved.*

Results: *The linear correlations between ACD and RS were not significant ($p > 0.05$). In the group with ACD < 2.8 mm, the mean refractive surprise using SRK-T, Haigis, Holladay 1, and Holladay 2 formulas were -0.191 ± 0.541, -0.189 ± 0.444, -0.201 ± 0.449, and -0.154 ± 0.489 D, respectively. In the group with ACD > 3.2 mm, the mean refractive surprise using the IOL formulas were -1.364 ± 0.541, -1.420 ± 0.541, 0.027 ± 0.394, and -0.045 ± 0.343 D, respectively.*

Conclusion: *The positive linear correlation between ACD and RS was weak. In eyes with ACD < 2.8 mm, the least RS was found with the Holladay 2 formula, while in eyes with ACD > 3.2 mm, this was found with Holladay 1.*

Keywords*: anterior chamber depth, cataract surgery, intraocular lens formula, refractive outcome, refractive surprise*

Introduction

Refractive outcome is a major factor in cataract surgery. In our modern era, a critical advancement is in the ability to estimate the power of the intraocular lens (IOL) that is to be implanted.[1] The power of IOL needed to produce the desired postoperative refraction outcome is determined by theoretical formulas such

Correspondence: Dr. Keith Ong, 2 Railway Ave, Eastwood NSW 2122, Australia.
E-mail: keithong@optusnet.com.au

as SRK/T (Sanders-Retzlaff-Kraff)/Theoretical), Haigis, and Holladay, prior to the cataract extraction.[2] Accurate biometric measurements of the eye and use of appropriate calculations have allowed surgeons to improve the predictability of refractive outcomes.

The parameter for diagnosing a shallow or deep eye is based on anterior chamber depth (ACD),[3] which represents the anatomical distance between the corneal endothelium and the anterior capsule of the crystalline lens.[4] In optical biometry, ACD is calculated from the corneal epithelium to the lens apex. Older mathematical formulas like SRK/T are determined by measurements of axial length (AL) and corneal curvature (K), with ACD as a surrogate that is estimated from keratometry; newer IOL implant power formulas like Haigis often involve measuring preoperative ACD.[1] The newer formulas theoretically yield lower prediction errors. This is because ACD is used to predict the postoperative effective lens position (ELP), which influences the postoperative refraction. However, refractive surprise (RS) can occur after surgery even if the modern formulae are used, especially for those with extreme myopia and extreme hypermetropia (*i.e.*, very large or very small eyes). It is known that IOL power calculations tend to yield hypermetropic refractive prediction errors in long eyes (large AL).[5] Therefore, RS are often anticipated for such extreme cases and targeting a bit of residual myopia[6] would help prevent hypermetropia post-cataract surgery.

The purpose of our study is to evaluate the influence of ACD on postoperative refractive outcomes by evaluating the RS of various IOL formulas after cataract surgery, comparing eyes with very shallow and very deep ACD.

Methods

In this prospective cohort study, 31 patients who had their cataract surgery with IOL implantation from January to December 2014 were included. Patients included are of Asian ethnicity and had attended a private ophthalmology clinical practice in Sydney, NSW, Australia. The cohort consists of 20 eyes with ACD less than 2.8 mm and 25 eyes with ACD greater than 3.2 mm. Patients' demographic details and biometric measurements were collected using IOLMaster 500 (Carl Zeiss Meditec AG; Germany), through which preoperative keratometry, ACD, and IOL lens power calculations were obtained using Carl Zeiss IOLMaster Advanced Technology V.7.5 software. The refractive outcomes were obtained from postoperative consultations at least one-month after cataract surgery.

We then analysed the clinical variables with regard to refractive outcomes using the SRK-T, Haigis, Holladay 1, and Holladay 2 IOL formulas. RS was calculated as the difference between the predicted postoperative refractions of different IOL formulas and the actual postoperative refraction achieved. Analysis of RS was done using Excel software (Microsoft; United States). Linear regression analysis

was performed using the method of least squares. A P value of less than 0.05 is considered significant; all tests were 2-tailed.[7]

Results

In the patient group with 20 eyes with small ACD (ACD < 2.8 mm), there were 13 patients with a mean age of 70 ± 6.96 years (55-86). Their average AL was 23.6 ± 1.352 mm (21.58-27.54) and mean ACD of 2.69 ± 0.117 mm (2.3-2.81). In the group with 25 eyes with large ACD (ACD > 3.2 mm), there were 18 patients with a mean age of 68 ± 5.91 years (58-79). Their average AL was 25.8 ± 1.28 mm (22.49-27.99) and mean ACD of 3.52 ± 0.218 mm (3.21-4.07). Across 31 patients, ACD increased significantly with AL, with a linear correlation of 0.497 ($p < 0.05$) (Fig. 1). The

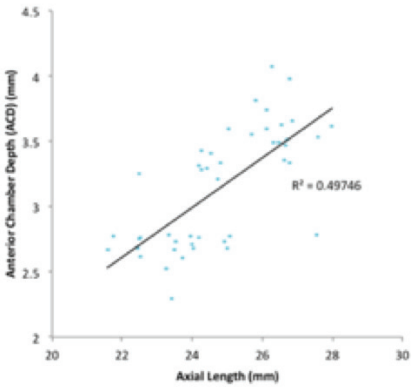

Fig 1. Relationship between AL and ACD in 45 Chinese eyes.

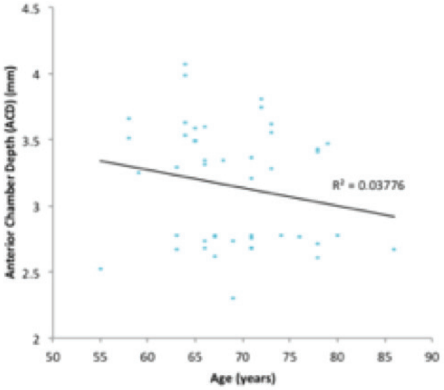

Fig 2. Relationship between age and ACD in 45 Chinese eyes.

Table 1. Preoperative characteristics of 20 shallow (ACD < 2.8 mm) and 25 deep (ACD > 3.2 mm) Chinese eyes

	Measure	Age (year)	IOL used (D)	Preop Refraction (D)	Postop Refraction (D)	AL (mm)	K (D)	ACD (mm)
Shallow eyes (ACD < 2.8 mm)	Mean	70	21.4	-0.313	-0.875	23.64	43.97	2.69
	SD	6.96	4.07	2.73	0.524	1.352	1.648	0.117
	Min	55	10	-2.75	-2.125	21.58	41.49	41.49
	Max	80	28.5	2.75	-0.25	27.54	46.59	46.59
Deep eyes (ACD < 3.2 mm)	Mean	68	15.9	-3.28	-1.47	25.76	43.84	3.52
	SD	5.91	3.85	3.97	0.519	1.282	1.204	0.218
	Min	58	11	-8.75	-2.25	24.18	41.86	3.25
	Mean	78	25.5	3.5	-0.5	27.99	46.85	4.07

Table 2. Mean postoperative RS using SRK-T, Haigis, Holladay 1, and Holladay 2 IOL formulas in 20 shallow (ACD < 2.8 mm) and 25 deep (ACD > 3.2 mm) Chinese eyes

ACD (mm)	IOL Formulas			
	SRK-T	Haigis	Holladay 1	Holladay 2
< 2.8	-0.191 ± 0.541	-0.189 ± 0.444	-0.201 ± 0.449	-0.154 ± 0.489
> 3.2	-1.364 ± 0.541	-1.420 ± 0.541	0.027 ± 0.394	-0.045 ± 0.343

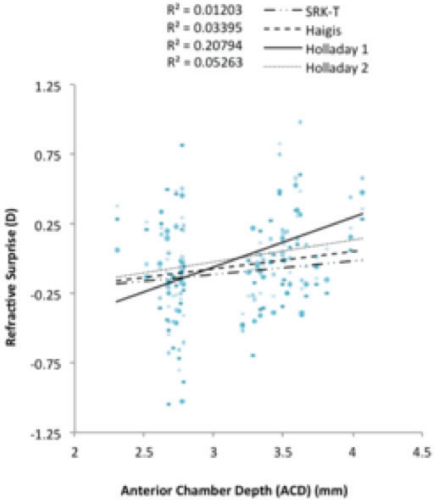

Fig 3. Relationship between postoperative RS and ACD in 45 Chinese eyes.

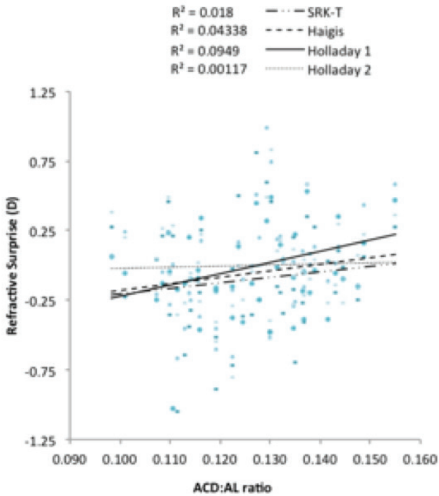

Fig 4. Relationship between ACD:AL ratio and postoperative RS in 45 Chinese eyes

decrease in ACD with aging was not significant in our study population (Fig. 2).

In eyes with ACD < 2.8 mm, the mean refraction was -0.313 ± 2.73 D preoperatively and -0.875 ± 0.524 D postoperatively (> 1-month) at follow-up (Table 1). The least RS was found with the Holladay 2 formula at -0.154 ± 0.489. In eyes with ACD > 3.2 mm, the mean refraction was -3.28 ± 3.97 D preoperatively and -1.47 ± 0.519 D postoperatively at follow-up (Table 2). The least RS was found with Holladay 1 at 0.027 ± 0.394 (Table 2). Overall, the increase in RS with increasing ACD was not significant. Linear regression analysis showed that the influence of ACD on RS was greatest using the Holladay 1 formula at R2 of 0.20794 ($p > 0.05$); the weakest correlation was attained using the SRK-T formula at R2 of 0.01203 ($p > 0.05$) (Fig. 3). Similarly, the correlations between the ACD:AL ratio and postoperative RS surprise using different IOL formulas were not significant, with R2 values of 0.018, 0.04338, 0.0949, and 0.00117 with the SRK-T, Haigis, Holladay 1, and Holladay 2 formulas, respectively (Fig. 4).

Discussion

The latest-generation IOL power prediction formulas have considerably improved refractive outcomes. The Holladay 1 and 2 and SRK/T formulas both use thin-lens theory, with different prediction algorithms for ELP and adjustment factors for short and long eyes;[8] the Haigis formula is based on exact thick-lens theory and does not use any other adjustment factors.[8] Nonetheless, there is still much controversy about which is significantly and consistently better.[9] Our study has found that the least RS was found with the Holladay 2 formula in small eyes with ACD < 2.8 mm and Holladay 1 in large eyes with ACD > 3.2 mm. This is consistent with other studies showing that the Holladay 2 formula should be used for patients with AL and corneal powers that are outside the normal ranges of 22-25 mm and 42-46 D.[2]

The SRK-T formula can predict refraction in patients with normal AL and ACD < 3 mm with less error and is preferred over other formulas.[10] However, the improved accuracy of prediction can also be a function of the surgeon's technical skills in implanting lenses consistently in a capsular bag.[1] Furthermore, we also have to consider the range besides the mean of RS when comparing different formulas. It has been found that the use of preoperative ACD in combination with AL for the precision of the pseudophakic ACD can be expected to improve the accuracy of IOL power calculation.[11] Our findings are consistent with their results, especially in Chinese eyes, which have more variable ACD.

Our results suggest that there is a tendency to have greater hypermetropic surprise in large ACD, as well as when ACD is disproportionately larger than AL. The Holladay 2 formula was found to have the least RS across all ACD:AL ratios, hence a practical suggestion would be to use the Holladay 2 formula for very shallow or deep eyes. Also, we know that ACD varies with age[12] as the lens thickens. However, ELP may not vary with age. ELP is known to influence the final refractive outcome and given there can be much variability in ELP among Chinese eyes, this can be a source of RS. Currently, ELP is estimated from AL and K readings.[13] Perhaps, estimating the distance from the corneal epithelium to the middle of the cataract lens rather than to the anterior capsule provides a better ELP estimate. We note that although ACD is defined as the anatomical distance between the corneal endothelium and the anterior capsule of the crystalline lens,[4] the IOLMaster 500 measures ACD as the distance from corneal apex to lens apex, hence including corneal thickness.[14] Modifying this measurement by taking it from the corneal epithelium to the centre of the cataract lens may provide a more accurate estimate of ELP. This may be possible in newer optical biometry instruments with swept source optical coherence tomography technology, as corneal thickness and cataract lens thickness can be measured. Perhaps we could modify IOL formulas by replacing the "ACD" in the formulas to a modified parameter

that can be called "*estimated ELP*", where estimated *ELP = ACD + ½(cataract lens thickness*). Further studies to evaluate this may help improve IOL formulas and minimise RS.

We also have to consider the range besides the mean RS when comparing different formulas. RS can be myopic or hypermetropic. There is much variation in refractive outcome, and RS can be difficult to predict in eyes that have small or large ACD. Our small study suggests small ACD causing myopic surprise and large ACD causing hypermetropic surprise. However, this is not significant, and the variability in RS means that there may be myopic or hypermetropic RS (which can range up to ± 0.75 D) in refractive outcomes in eyes with small and large ACD. Hence, it may be prudent to select an IOL power that aims for a refractive outcome of -0.5 to -0.75 D in order to avoid a hypermetropic refractive outcome after cataract surgery.

In conclusion, in eyes with ACD < 2.8 mm, the least RS was found with the Holladay 2 formula, while in eyes with ACD > 3.2 mm, this was found with the Holladay 1. Overall, the Holladay 2 formula was found to have the least postoperative RS across all ACD:AL ratios. The positive linear correlation between ACD and RS was weak. As ELP is known to influence RS, replacing "ACD" in the IOL formulas with a modified parameter tentatively known as "estimated ELP" may improve refractive outcomes. Further studies are needed to elucidate the relationship accurately.

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Evaluation of anterior chamber volume using Pentacam and anterior segment optical coherence tomography among normal subjects

Vijaya Anandan[1,2], Rekha Srinivasan[1], Rashima Asokan[1,2], Ronnie George[2]

[1]Elite School of Optometry, Chennai, India; [2]Medical Research Foundation, Chennai, India

Abstract

Aim: *To compare the anterior chamber volume measurements obtained with Pentacam and derived from anterior segment optical coherence tomography.*

Design: *Cross-sectional study.*

Methods: *We included normal subjects who underwent a comprehensive eye examination including refraction, keratometry, Goldmann applanation tonometry, gonioscopy, anterior segment optical coherence tomography (AS-OCT) (Carl Zeiss Meditec Inc.; Dublin, CA, USA) and Pentacam (Oculus Inc.; Lynnwood, WA, USA). Fifty scans were selected for Pentacam and 12 images were selected for calculation of anterior chamber volume. Only the right eye was considered for analysis.*

Results: *One-hundred and nineteen eyes of 119 subjects were included for analysis. The mean age of the subjects was 42.58 ± 13.15 years, of which 74 were female and 45 were male. The mean anterior chamber volume measured using AS-OCT was 119.17 ± 26.56 mm3 and with Pentacam was 131.29 ± 34.26 mm3. The comparison of means between the two modalities was statistically significant (t = -8.857, Mean Difference (MD) = 12.11, 95% CI: (4.29, 19.95), p = 0.003). Bland-Altman plot showed poor agreement between the chamber volume measurements obtained by Pentacam and AS-OCT with MD of 12.1 mm3 (95 % CI: 41.4 to -17.1) and intra-class correlation between the two instruments was 0.94 (95% CI: 0.91, 0.96) (p < 0.0001).*

Conclusion: *The anterior chamber volume can be measured using Pentacam as well as AS-OCT since these measurements were reliable. However, these measurements were not interchangeable due to poor levels of agreement.*

Keywords*: anterior chamber volume, Pentacam, optical coherence tomography (OCT)*

Introduction

Evaluation of anterior chamber parameters is essential for ophthalmic evaluation. Slit lamp examination is of help for anterior segment examination. Objective and

Correspondence: Dr Ronnie George, Medical Research Foundation, Sankara Nethralaya, 18, College Road, Chennai 600 006, India.
E-mail: drrg@snmail.org

quantitative information regarding the angle structures can be found with the help of gonioscopic lenses. However, the procedure is examiner dependent and the findings are subject to variability. Furthermore, they do not provide quantitative information regarding the angle structures and angle parameters for further follow-up examination. New anterior segment imaging techniques overcomes these difficulties. Anterior chamber measurements can be measured using biometry and ultrasound biomicroscopy as contact procedures and anterior segment optical coherence tomography (AS-OCT) and Pentacam as non-contact procedures. These instruments give us the quantitative measurements of cornea, anterior chamber, iris, angle structures, and lens. The information provided by these techniques helps clinicians in understanding the quantitative and qualitative information about the anatomic relationships of the anterior segment. These instruments provide information such as angle, depth measurement, and volume of the anterior segment.

The assessment of anterior chamber volume (ACV) helps us in understanding the mechanism of aqueous humour dynamics and has relevance in primary angle-closure glaucoma and pigmentary glaucoma. Fluorometry is considered to be the gold standard in assessing ACV.[1] This procedure is invasive and actually gives aqueous volume rather than ACV. The available devices used for measuring ACV are the Pentacam (Oculus Inc.; Lynnwood, WA, USA) and the Visante OCT (Carl Zeiss Meditec Inc.; Dublin, CA, USA).

Pentacam uses the Scheimpflug principle to obtain images of the anterior segment. It takes up to 50 scans of the anterior segment in less than 2 seconds. It calculates data for corneal topography (anterior and posterior corneal surface) and thickness, anterior chamber depth, lens opacification, and lens thickness. The Pentacam-Scheimpflug requires minimal experience for image acquisition. When correct alignment and focus with the patient's cornea has been achieved, it has an inbuilt function which automatically gets started.

AS-OCT is a non-contact procedure that is performed in the sitting position. With a spatial resolution of 10-20 μm, the Visante OCT is a non-contact optical system that uses a 1310 nm super luminescent diode to image the anterior chamber of the eye. It is easy to operate and allows view of both angles simultaneously and the iris-lens interaction, providing anterior segment scans, high-resolution corneal and anterior chamber angle scans, and pachymetry maps both relative and differential at a rate of up to 2048 A-scans per second. It gives information on depth, width, and anterior chamber angle. It has an optical axial resolution of up to 18 mm and transverse resolution of up to 60 mm. Imaging of opaque corneas is possible and minimal experience is required for image acquisition. ACV can be derived from the measurements using custom-designed software.

Various studies have reported the ACV measurements with Pentacam and

AS-OCT.[2,3] The repeatability and reproducibility in measuring anterior chamber parameters between these studies remains unclear, with Yi *et al.*[4] and Labiris *et al.*[5] reporting good agreement with Pentacam and AS-OCT measurements, but Fu *et al.*[7,10] reporting poor agreement between these devices. To the best of our knowledge, no studies have reported on the measurement of ACV using AS-OCT and Pentacam in the Indian population. Thus, the aim of our study is to understand the comparison of ACV measurements using Visante OCT and Pentacam.

Materials and methods

Subject selection

The study was a cross-sectional study. Normal subjects with no evidence of previous ocular trauma and ocular surgeries were included in the study. All the normal participants underwent a comprehensive eye examination including refraction, keratometry (KMS-6; Appaswamy Associates; Chennai, India), Goldmann applanation tonometry, gonioscopy, Visante AS-OCT, and Pentacam. Sample size calculation was based on a study by Fu *et al.* The study was approved by the Ethics Committee and adhered to the tenets of the Declaration of Helsinki and written informed consent was acquired from all the participants.

Measurement of ACV using Pentacam

ACV was assessed by Pentacam. Fifty scans were selected for the better assessment of the anterior chamber parameters. The test was done without dilation. From the recorded Scheimpflug images, the system calculates a Virtual Eye of the anterior eye segment. From this, all further information such as the anterior chamber analysis, topography, pachymetry, etc. are calculated. After image acquisition, the instrument automatically calculates the measurements of anterior chamber, namely, chamber height endothelium, chamber height epithelium, chamber angle, chamber angle minimum, chamber angle position dependent, chamber angle superior/inferior/nasal/temporal position, and chamber volume (mm^3). All these measurements were exported into an Excel sheet. The images with poor quality score were excluded.

Measurement of ACV using AS-OCT

Visante AS-OCT was used to assess the anterior chamber parameters. The instrument scans four meridians and displays it in a single screen, enabling the examiner to visualize eight meridian angles at a time. The scan can be adjusted to visualize other meridians. The default scan meridians are 0°-80°, 45°-225°, 90°-270°, and 135°-315°. All the scans were focused on the pupillary centre to visualize the angles. Twelve scans were taken with 15° intervals. AS-OCT images image that did not have good quality were excluded as the volume information is dependent on

image quality. Images with poor reflectivity, poor brightness, poor outline, poor centration, and with no angle insertion were considered of poor quality.

Calculation of ACV

The images were obtained from the Zeiss Visante AS-OCT. Images were taken directly from the equipment's output function (816 × 636 pixel) in JPEG format.

Image processing

Images were analysed using MATLAB 7.0 (MathWorks; Natlick, MA, USA) to calculate the ACV. The anterior chamber details alone were cropped, the image was enhanced by noise reduction, and image contrast was improved. The observer marked the pupillary border on either side using the mouse. Once the pupillary border was selected, ACV was calculated based on integration.

The calculation of the entire ACV was similarly done using the shell method of integration.[3]

$$V = 2\pi \int_a^b x\, f(x)\, dx$$

Each scan was subjected to this formula and the ACV was calculated. A total of 12 scans per eye was performed and the average of all calculated ACV was calculated. The mean ACV calculated was considered as the final ACV of that eye. All the measurement markings were done by a single trained examiner.

Statistical analysis

Statistical analysis was performed using SPSS version 14.0 (SPSS Inc.; Chicago, USA) and Medcalc version 8.1.0 (Medcalc software; Mariakerke, Belgium). The Kolmogorov Smirnov test was used to assess the normality of the data. Significance level was kept at 5%. The independent t-test was done to compare the means of ACV between Pentacam and AS-OCT as well as the mean ACV between

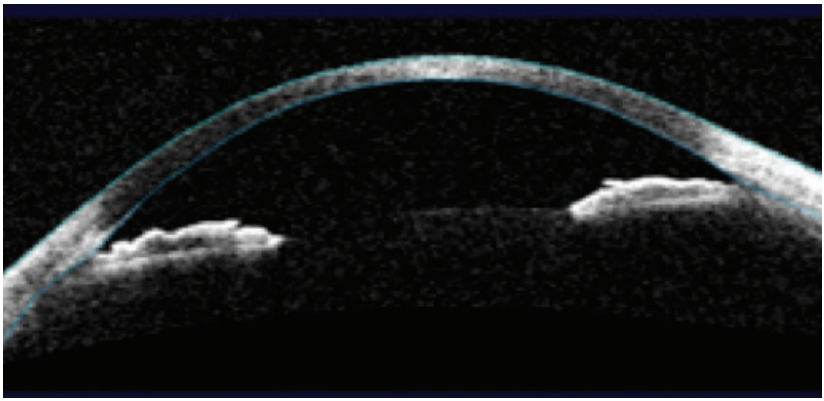

Fig. 1. Input image of the anterior chamber into the Matlab window.

males and females with these two modalities. Pearson and intra-class correlation (ICC) were performed to find out the correlation of ACV obtained by the two instruments. Bland-Altman analysis was done to find the levels of agreement between the two instruments. Only the right eye was considered for analysis.

Results

One hundred and nineteen eyes of 119 subjects were considered for analysis. The mean age of the subjects was 42.58 ± 13.15 years, out of which 74 were females and 45 were males. The mean ACV volume measured using AS-OCT was 119.17 ± 26.56 mm^3 and with Pentacam was 131.29 ± 34.26 mm^3. The mean ACV between males and females is given in Table 1, where no significant difference was found between males and females with these two modalities. The comparison of means of ACV with the two instruments was statistically significant (t = -8.857, Mean Difference = -12.11, 95% CI: [-14.82, -9.40], $p < 0.001$). The correlation between the chamber volumes between the two instruments was r = 0.91 ($p < 0.0001$). ICC between the two instruments was 0.94 (95% CI: 0.91, 0.96) ($p < 0.0001$) with Cronbach's alpha value of 0.94 ($p < 0.0001$).

Table 1. Comparison of ACV between males and females with the two modalities

Modalities	Mean ACV of males (Mean ± SD) (mm^3)	Mean ACV of females (Mean ± SD) (mm^3)	Mean Difference (95% CI)*	p-value
Pentacam	134.08 ± 36.53	129.59 ± 32.96	4.494 (-8.364, 17.352)	0.490
AS-OCT	121.56 ± 26.67	117.72 ± 26.56	3.831 (-6.130, 13.792)	0.448

ACV: anterior chamber volume; SD: standard deviation; CI: confidence intervals; *independent t-test significance level ($p < 0.05$)

Limits of agreement between the two instruments

The Bland-Altman plot showed poor agreement between the chamber volume measurements obtained by Pentacam and AS-OCT with Mean Difference of 12.1 mm^3 (shown in Fig. 2) (limits of agreement: 41.4 to -17.1)

Discussion

ACV measurement provides quantitative information regarding the anterior segment. The current study involves ACV measurement with AS-OCT using Matlab software, which was used to mark the anterior chamber border and then calculate the volume. The current study has a larger sample size in accordance to the ACV in existing literature, as shown in Table 2.

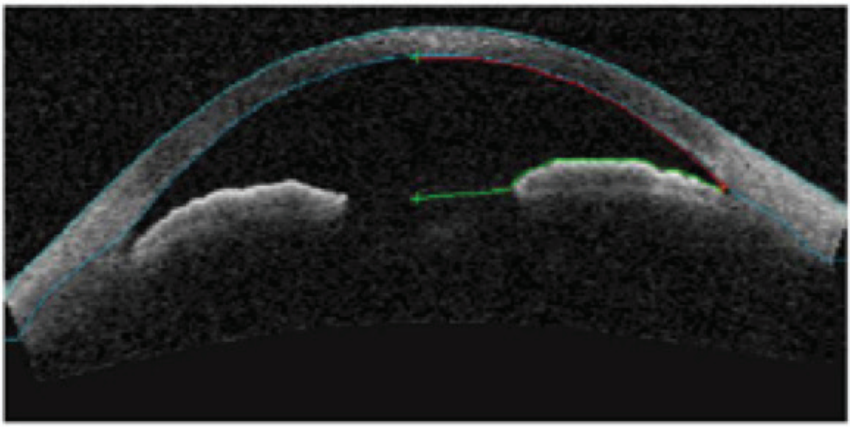

Fig. 2. Marking of anterior the chamber and pupillary border with the calculation of ACV.

Table 2. Comparison of sample size with existing literature

Study details	Sample size
Wang *et al.* (2007)[3]	24
Labiris *et al.* (2009)[5]	20
Fukuda *et al.* (2011)[6]	40
Fu *et al.* (2010)[7]	50
Fu *et al.* (2010)[10]	39
Current study	119

Studies have reported the repeatability and reproducibility of these two instruments.[3,5,6] In our study, the measurements were taken by a single trained examiner. An average of three readings was taken for Pentacam and an average of 12 scans[3] was considered for AS-OCT. When the averages of these two modalities were compared, the ACV measured by Pentacam was 12.11 mm^3 more than that measured by AS-OCT. This finding was consistent with Fukuda *et al.*,[6] who evaluated the repeatability and reproducibility of ACV obtained using 3-D corneal and anterior segment optical coherence tomography (CAS-OCT) and dual Scheimpflug imaging, where CAS-OCT ACV was 8 mm^3 less than Scheimpflug imaging. The smaller difference could be related to CAS-OCT having a mean axial resolution of 11 microns, whereas the Visante AS-OCT has a mean axial resolution of 18 microns. Fu *et al.*[7] showed that Pentacam ACV measurements were 14.21 µL less than values given by AS-OCT. Labiris *et al.*[5] have showed that there is no difference between ACV measured by Pentacam and AS-OCT. Our study found a difference in ACV as measured between the two modalities. Furthermore, the

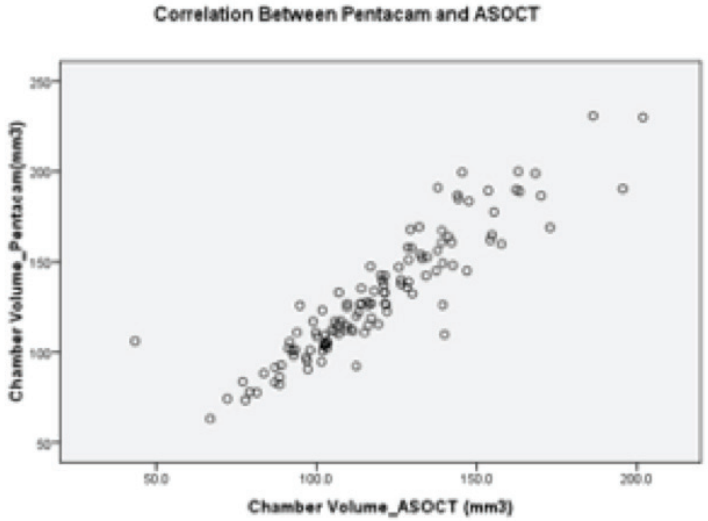

Fig. 3. Scatter plot showing the correlation of ACV measurements between Pentacam and AS-OCT.

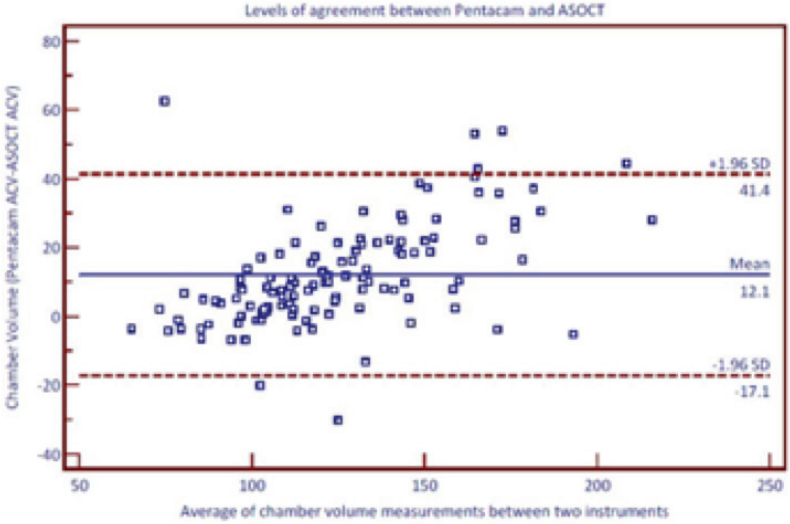

Fig. 4. Bland-Altman plot of difference in chamber volume measurements between Pentacam and AS-OCT and average of chamber volume measurements between the two measurements.

mean ACV values found in our study were less when compared to other studies. This could be due to the shorter axial lengths and shallower anterior chamber depths in Indian eyes compared to other ethnicities.[8,9] In our study, no significant difference in ACV was noted between males and females; however, true values of ACV for females were lesser than males. Another study by Fu *et al.*[10] also proposed that Pentacam ACV measurements are less than AS-OCT ACV measurements by 11.8 µL. The differences in mean difference between these studies are seen because of the varied sample size of the two studies. The difference between Pentacam and AS-OCT measurements found in our current study could possibly be due to the ethnic differences between the Chinese and Indian population.[9]

There was a poor agreement between the ACV measured by Pentacam and AS-OCT. The mean difference was 12.11 mm^3, with wider limits of agreements from -17.1 mm^3 to 41.4 mm^3, which fall outside clinically acceptable levels.[6,7,10] The measurements of ACV with Pentacam and AS-OCT correlated well ($r = 0.91$, $p < 0.001$) and were repeatable, with an ICC value of 0.94. Although the ACV measured by these instruments is repeatable, it is not interchangeable due to the large difference in mean values and the large width in confidence interval limits. This could be due to the differences in measurement methods between the two devices. Pentacam uses the Scheimpflug principle, where the light of the instrument does not penetrate the corneoscleral limbus, thereby giving interpolated values by extending the lines of the cornea and iris border with that of the angle, which can overestimate ACV measurements. In our study, both the comparison of means and levels of agreement analysis showed that the measurements of ACV given by these modalities were statistically different, in accordance with studies by Fu *et al.*[7,10] Apart from all, this study provides a better estimate of ACV when compared to other studies. Our study has a few limitations. Intersession repeatability between the two instruments was not studied, which could explain the difference in ACV over a period of time (diurnal variation) examined by a single examiner. Although the sample size was large when compared to other studies, there is no normative data reference for the mean values of different ethnicities and thus, grading of shallow or deep eyes becomes difficult. The ACV calculated could be erroneous if the image was decentred or of poor quality. If image scaling is irregular, the calculation of the volume would be highly variable.

Conclusion

AS-OCT can be used to measure ACV since the measurements provided by these modalities correlate with each other. However, the levels of agreement between these modalities are not sufficient to allow these instruments to be comparable.

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Original Article

Prevalence of glaucoma in first-degree relatives of patients with primary open-angle glaucoma and normal-tension glaucoma

Preeti Gupta, Vijaya Pai H.
Department of Ophthalmology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Karnataka, India

Abstract

Objective: *To determine the prevalence of glaucoma in first-degree relatives of patients with primary open-angle glaucoma (POAG) and normal tension glaucoma (NTG).*

Methods: *Observational study of first-degree relatives of patients with POAG and NTG who were screened for glaucoma.*

Results: *A total of 66 first-degree relatives of patients with glaucoma (POAG/NTG) were included in the study. We found a prevalence rate of 16.6%: 13.6% were diagnosed to have the disease and 3% were newly detected to have glaucoma during the study. We found that although 66.7% of the subjects were aware of the family history of glaucoma, only 36.4% were aware that they were at increased risk of developing glaucoma.*

Conclusion: *In our study, we found high prevalence of glaucoma in first-degree relatives of patients with glaucoma. This highlights the importance of selective screening of high-risk groups such as first-degree relatives of patients with POAG/NTG.*

Keywords*: awareness, first-degree relatives, glaucoma, increased risk, prevalence*

Introduction

Glaucoma is the most common cause of irreversible blindness worldwide.[1] In southern India, the prevalence of open-angle glaucoma is estimated to be 1.6% of the population, with more than 98% being unaware that they have the disease.[2]

Primary open-angle glaucoma (POAG) has a genetic or familial component. It is believed that the genetic influence occurs through polygenic or multifactorial transmission. Reportedly, 5–50% of cases of POAG are hereditary, with the best estimate being 20–25%. The risk of developing POAG in first-degree relatives is 4–16%.[3-5] The disease has a hereditary component and becomes more prevalent with age.

POAG progresses very slowly and is usually asymptomatic until late in its course, so affected individuals can develop severe damage before they seek professional help. POAG has been shown to be more prevalent in first-degree relatives, so

Correspondence: Dr. Preeti Gupta, 705, Residential Quarters, Institute of Liver and Biliary Sciences,Vasant Kunj D1, New Delhi-110070, India
E-mail: drpreetigupta82@gmail.com

their screening for glaucoma is important. Various studies have reported different prevalence depending on the population sampled, the age of the individuals studied, the techniques of examination, and the definitions of glaucoma used.

Methods

This was a prospective study of first-degree relatives (parents, siblings, and offspring) of patients with POAG and normal tension glaucoma (NTG). Patients with POAG or NTG were requested to give contact details of their first-degree relatives. These first-degree relatives were then contacted and requested to get screening tests for glaucoma done. Informed consent was taken from all the subjects. The study was approved by the hospital ethics committee.

Those with media opacity due to which fundus could not be visualized or perimetry could not be done, or patients with other macular or neurological problems that could affect the test results were excluded from the study.

Subjects underwent detailed ophthalmic examination including visual acuity (using Snellen's chart), slit lamp examination, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, gonioscopy using Goldmann single mirror gonioscope, and fundus examination with a 90 D lens. Pachymetry was done using the Alcon Ocuscan RxP ultrasound pachymeter. In cases where disc findings were suspicious, visual field analysis was done using the Zeiss Humphrey Field Analyser Model 750. When the visual field showed glaucomatous defects, a second field was repeated to confirm the presence of the defects. Glaucomatous disc changes included vertical C:D ratio > 0.6, focal notch, NRR < 0.1 in superior or inferior quadrant, disc haemorrhage, nerve fibre layer loss, and cup asymmetry between the two eyes of > 0.2 when disc size was the same for both eyes. Subjects were labelled as having glaucoma when the field defect met Anderson's criteria for glaucoma diagnosis. Subjects were also asked if they knew the fact that their first-degree relative suffered from glaucoma and the response was noted. Subjects were also asked if they knew that being first-degree relatives of a patient with glaucoma increased their risk of developing glaucoma.

On the basis of test results participants were classified as:

1. Definite glaucoma: glaucomatous disc with corresponding field defect and/or IOP ≥ 21 mmHg.
2. Glaucoma suspects: normal HFA, but IOP ≥ 21 mmHg and/or suspicious, but not unequivocally glaucomatous disc appearance.
3. Normal: normal optic disc, IOP < 21 mmHg.

Results

A total of 66 subjects who satisfied the inclusion and exclusion criteria were included in the study. The age of the subjects ranged from 19-80 years with a

mean age of 49.6 ± 12.5 years. The study population included 38 males (58%) and 28 females (42%). Of the 66 first-degree relatives examined during the study, 23 were siblings (34.8%) and 43 were offspring (65.2%). In our study, there were no parents.

Forty-four subjects (66.7%) were aware of the fact that their first-degree relative had glaucoma and 42 (63.6%) subjects responded negatively when inquired if they knew they were at increased risk for developing glaucoma. Nine subjects were already diagnosed as POAG/NTG and five cases as glaucoma suspects, shown in Table 1. Of the 14 patients classified as glaucoma and glaucoma suspects, 10 (71.4%) were males and 4 (28.6%) were females. Seven were siblings and seven were offspring of POAG/NTG patients. Table 2 shows 17 subjects were newly diagnosed as either POAG/NTG (2) or glaucoma suspects (15). Overall, our study categorized a total of 66 subjects, as shown in Table 3.

Thus, in our study we found the prevalence of glaucoma in first-degree relatives to be 16.7% with an additional 30.3% subjects as glaucoma suspects. Of the total 11 glaucoma subjects diagnosed, 8 were siblings while 3 were offspring.

Table 1. Subjects already diagnosed as glaucoma and glaucoma suspects

	Frequency	Percentage (%)
Glaucoma suspect	5	35.7
Glaucoma	9	64.3
Total	14	100.0

Table 2. Subjects newly diagnosed as glaucoma and glaucoma suspects

	Frequency	Percentage (%)
Suspect	15	88.2
POAG/NTG	2	11.76

Table 3. Total number of subjects included in the study

	Frequency	Percentage (%)
Normal	35	53.0
Suspect	20	30.3
Glaucoma	11	16.7
Total	66	100.0

Discussion

Positive family history is an important risk factor for the development of POAG.[3,4] Early detection of the disease is crucial in slowing down glaucomatous damage

and minimizing irreversible vision loss, but an effective mass screening program for glaucoma has not yet been developed. One possible strategy for enhancing the effectiveness of glaucoma screening programs is to focus on high-risk populations such as those who have a family history of the disease.

We included all first-degree relatives of patients with a family history of POAG/NTG willing to participate in our study irrespective of age. In the Glaucoma Inheritance Study in Tasmania,[3] all the relatives were included in the study, with age ranging from 13 to 97 years. We included all first-degree relatives who were willing to come to the hospital for examination in our study. Age range in our study was 19-80 years. Other studies set a lower age limit for subjects to be included: in Vegini *et al.*[5] the lower limit was 30 years; in Nguyen *et al.*[6] the lower limit was 35 years; and in the Beaver Dam Eye study the lower limit was 43 years.[7] We included all first-degree relatives in our study, which may affect the study outcome, as young subjects are less likely to develop glaucoma and therefore project a lower prevalence.

The average age of the study population was 49.6 years (S.D 12.5) with a median of 48.5 years, similar to studies done by Vegini *et al.*[5] and Nguyen *et al.*,[6] but lower than many other studies.[3,4,8] Our study included 34.8 % siblings and 65.2% offspring.

The Glaucoma Inheritance Study in Tasmania[5] and other states in Australia examined 442 individuals from five pedigrees with a strong positive family history of POAG (not only first-degree relatives), of which 11% had a prior diagnosis of POAG, 2% had glaucoma-suspect status, and 16% were newly diagnosed (7% POAG and 9% suspects). Prevalence rate in first-degree relatives was 38.6%. We found a prevalence rate of glaucoma of 16.7% with 13.6% previously diagnosed and 3% as newly diagnosed cases. This variation in the prevalence may be due to the fact that the Glaucoma Inheritance study in Tasmania was a broad-based study with a large subject size, so most of the first-degree relatives were included in the study.

The Rotterdam Eye Study[8] investigated the familial aggregation of POAG by examining the first-degree relatives (siblings and children) of 45 of the 48 cases of glaucoma identified, as well as a matched set of controls. The prevalence of glaucoma was 10.4% in siblings of patients and 1.1% in offspring of patients. This is similar to our study, where we found a prevalence rate of 12.1 % in siblings of patients and 4.5 % in offspring of patients.

The study by Nguyen *et al.*[6] examined 86 relatives from 15 families with chronic open-angle glaucoma (OAG), including 50 first-degree relatives. In these 50 first-degree relatives, 11 siblings (22%), 4 children (8%), and 3 (6%) parents were diagnosed with glaucoma, for a total glaucoma prevalence rate of 36% in first-degree relatives. The difference in the results may be due to the fact that the study

done by Nguyen tried to include most of the relatives in these families, while in our study not all first-degree relatives could be included in the study.

The Barbados Family Study[4] investigated the potential role of inheritance of OAG among families of African origin. A total number of 1056 relatives were included in the study, of which 865 were first-degree relatives (21 parents, 181 full sibling, 157 half sibling, and 506 offspring). Prevalence rates among them was 0.9% for parents, 4.5% for full sibling, 3.23% for half sibling, and 1.3% for offspring. The difference in our study results could be due to the fact that not all first-degree relatives were included in the study; racial factors might also play a role.

The study by Vegini *et al.*[5] examined 101 first-degree relatives accompanying POAG patients to the hospital. They found the prevalence rate of glaucoma among these first-degree relatives to be 16.8%, with 10.9% previously diagnosed cases and 5.9% freshly diagnosed cases. This result is similar to our study, where we found a prevalence rate of 16.6 %, with 13.6% previously diagnosed cases and 3% newly diagnosed cases.

In a study by Kong *et al.*[9] of 531 first-degree relatives screened, 67 (12.62%) were identified to have POAG, a rate eight times higher than that of the control group (8 of 526, 1.52%). The effect of family history on parents, siblings, and offspring of probands was statistically significant, with OR values of 6.92 (95% CI: 1.90–25.18), 11.29 (95% CI: 3.63–35.11), and 11.35 (95% CI: 1.69–76.21), respectively. In the case of glaucoma suspects, a significant effect was found for both family units (OR 5.60; 95% CI: 1.15–27.21) and offspring (10.83 OR; 95% CI: 1.34–87.73).

In a south Indian study by Rajendrababu *et al.*[10] of 514 first-degree relatives of POAG patients examined, 68 (13.3%) had definite glaucoma while another 28 (5.5%) were either ocular hypertension or glaucoma suspects. This result shows nearly similar prevalence rates to our study.

Limitations of our study include the small sample size and the fact that we could not include all first-degree relatives of glaucoma patients, therefore the results might not reflect the actual prevalence. The reasons why not all first-degree relatives could be included were: migration of relatives to different cities, inability to come to the hospital for examination, and lack of interest for the examination. This again projects the difficulty in screening all first-degree relatives of glaucoma patients. Furthermore, we compared our results mostly with non-Asian countries, which may also account for a difference in prevalence rates.

Our study found that 66.7% of the subjects were aware of the family history of glaucoma, but only 36.4% were aware that they were at increased risk of developing glaucoma. In a study by Friedman *et al.*[11] among 102 probands and 100 (of 230 eligible) family members who were interviewed, 21% of both groups were not aware that OAG is hereditary. This shows the lack of awareness about increased hereditary risk of glaucoma among the general population. Although the subjects

were aware of the fact that their relative had glaucoma, they did not know that they were at increased risk and needed to undergo glaucoma screening.

Our study emphasizes the need for screening first-degree relatives of patients with POAG/ NTG. Selective screening of first-degree relatives of POAG/NTG patients helps in early disease diagnosis. We also need a large population-based study to find out the prevalence rates of glaucoma in relatives of glaucoma patients among the Indian population.

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Prevalence of ocular surface disease in patients with glaucoma on topical medications

Vijaya Pai H[1], L Satya Hareesh Reddy[1]
[1]Department of Ophthalmology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India

Abstract

Aim: *To compare the prevalence of ocular surface disease (OSD) in patients using antiglaucoma medications vs normal subjects.*

Design: *Prospective observational study.*

Method: *A total of 94 patients with glaucoma on topical medications were included in the study group. Age- and gender-matched normal subjects (n = 94) formed the control group. They were assessed for OSD using ocular surface disease index (OSDI) questionnaire, tear break-up time (TBUT), Lissamine green staining, and Schirmer's test.*

Results: *The prevalence of OSD was significantly more in the study group (72.4%) when compared to controls (44.6%) using the OSDI questionnaire. Schirmer's test showed 84% patients had decreased tear production in the study group vs 53% in controls. TBUT was abnormal in 67.1% of the study group and of 47.8% controls. Lissamine green staining was positive in 36.2% of patients in the study group and 31.8% of controls.*

Conclusion: *OSD was more common in patients using intraocular pressure (IOP)-lowering drugs than in controls. Long-term therapy and multiple medications were associated with severe OSD.*

Keywords*: antiglaucoma medications; dry eye; ocular surface disease index (OSDI); preservatives*

Introduction

Topical hypotensive medications remain the standard form of therapy for glaucoma. Intraocular pressure (IOP)-lowering medications are multidose medications and include preservatives to prevent microbial contamination and biodegradation, thus maintaining drug potency and prolonging its shelf life.[1,2]

As glaucoma is a disease of the elderly, they are more prone to developing ocular surface disease (OSD). Prevalence of OSD in people over 40 years is 2.1%, ranging from 0.3% in people aged 40 years to 3.3% in people aged 70 years.[3] Glaucoma patients have to be treated with topical medications that contain preservatives and cause increased tear evaporation, inducing an immunological and/or toxic response from the ocular surface.[4]

Correspondence: Dr. Vijaya Pai H, Department of Ophthalmology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, 576104, India.
E-mail: paivijaya@yahoo.co.in

Methods

This was a prospective observational study conducted at a tertiary care center during the period between August 2013 and September 2015. Patients with glaucoma (n = 94) formed the study group; age- and gender-matched normal subjects (n = 94) who were not on any topical medications formed the control group. Sample size was estimated based on the minimum expected prevalence of 40% (based on the literature). In order to estimate this prevalence with 25% allowable error and 95% confidence, the required sample size was estimated to be a minimum of 93.

The study was cleared by the institutional ethical committee. Patients with primary open angle glaucoma, primary angle closure glaucoma, combined mechanism glaucoma, pseudoexfoliation, and pigment dispersion glaucoma using topical antiglaucoma medications for more than six months were recruited. Patients who were using topical medications like steroids and lubricants, those who had undergone any ocular surgery, and patients with lens-induced glaucoma and glaucoma secondary to uveitis were excluded from the study. Information regarding the number of eye medications for glaucoma and duration of treatment was collected.

Patients were assessed for OSD using the following tests in the order given below.

1. Ocular surface disease index questionnaire (OSDI)
   The OSDI is a disease-specific questionnaire used to quantify the specific impact of dry eye on vision related quality of life. The total OSDI score is calculated using the formula:

$$\text{OSDI} = \frac{\text{Sum of scores for all the questions asked}}{\text{Total number of questions answered}} \times 25$$

   Using OSDI scores, patients were categorized as: normal (score 0-12), mild symptoms (13-22), moderate symptoms (23-32), and severe symptoms (33-100).[5]
2. Tear film break-up time (TBUT)
   TBUT was evaluated by measuring the interval between the last blink and the appearance of the first area of tear film break-up on the corneal tear film using a cobalt blue filter on the slit lamp microscope. The results were graded as: more than ≥ 10 seconds: normal; 5-9 seconds: mild to moderate; < 5 seconds: severe
3. Lissamine green staining of cornea and conjunctiva
   Lissamine green staining was done by instilling one drop of Lissamine green into the lower conjunctival sac. Staining of the ocular surface was evaluated

after 30 seconds but before 2 minutes had elapsed after the instillation. It was graded using the Oxford Scheme as: 0-1: normal; 2-3: mild to moderate; and 4-5: severe.

4. Schirmer's test
   Schirmer's test 1 (without anaesthesia) was done by placing a Whatmann no. 41 filter paper in the lower cul-de-sac over the junction of the outer and middle third of the lower lid. Readings were noted after five minutes. Values were classified as: above 10 mm: normal; 6 to 10 mm: mild to moderate; and < 5 mm: severe tear deficiency.

Results

A total of 94 patients with glaucoma and 94 controls were included in the study. Among the patients with glaucoma, 61 (64.9%) were males and 33 (35.1%) were females. Among controls, 61 (64.9%) were males and 33 (35.1%) were females.

Mean age of the glaucoma patients was 63.5 ± 10 years, ranging from 26 to 92 years. Mean age of controls was 62.3 ± 10.7 years, ranging from 29 to 82 years. Twenty-six patients (27.7%) were on treatment for less than or equal to one year, 37 patients (39.4%) for 2-5 years, 20 patients (21.3%) for 6-10 years, and 11 patients (11.7%) were on treatment for more than 10 years.

Among glaucoma patients, 68 (72.4%) patients had symptoms of OSD on the OSDI questionnaire. Of those, 62 patients (66%) had mild to moderate symptoms and 6 patients (6.4%) had severe symptoms. Schirmer's test showed decreased tear production in 79 patients (84%). Among them, 44 patients (46.8%) had mild to moderate decrease in tear production while severe deficiency was seen in 35 patients (37.2%). TBUT was abnormal in 63 patients (67.1%). Lissamine green staining was positive in 34 patients (36.2%), of which 33 patients (35.1%) had mild to moderate staining and 1 patient (1.1%) had severe staining (Table 1).

Table 1. Tests results of patients on topical IOP lowering medications

Results	OSD (%)	Schirmer's test (%)	TBUT (%)	Lissamine green staining (%)
Normal	27.7	16	33	63.8
Mild-Moderate	66	46.8	62.8	35.1
Severe	6.4	37.2	4.3	1.1

Fifty-two patients were on treatment with more than one antiglaucoma medication. With increased number of medications, from one or two to three or four, the mean OSDI score increased from mild (19.6) to moderate (23.1), respectively,

although it was not statistically significant (p = 0.183, independent sample t-test) (Table 2).

Table 2. Mean OSDI score in relation to number of medications

Number of drugs	Number of patients	Mean OSDI score	Std deviation
1 to 2	79	19.6203	9.59
3 to 4	15	23.1333	7.36

P = 0.183, Independent sample t-test

The mean OSDI score in patients using medications for less than five years was 16.5, indicating mild OSD, and in patients using medications for more than five years it was 27.1, indicating moderate OSD. The difference (p = 0.00) was statistically significant (Independent sample t-test) (Table 3). With increased duration of treatment and number of medications, test results became more positive (Tables 4-7).

Table 3. Mean OSDI score in relation to treatment duration

Treatment duration	Number of patients	Mean OSDI score	Std deviation
< 5 years	62	16.5806	8.33
> 5 years	32	27.1562	6.93

P = 0.000, Independent sample t-test

Table 4. Correlation between treatment duration and tests

Treatment duration (years)	Number of patients	OSDI%			Schirmer's test %		
		Normal	Mild-moderate	Severe	Normal	Mild-moderate	Severe
≤ 1	26	17 65.4%	9 34.6%	0 0%	10 38.5%	9 34.6%	7 26.9%
2–5	37	8 21.6%	29 78.4%	0 0%	4 10.8%	23 62.2%	10 27%
6-10	20	1 5%	17 85%	2 10%	1 5%	10 50%	9 45%
> 10	11	0 0%	7 63.6%	4 36.4%	0 0%	2 18.2%	9 81.8%

Table 5. Results of TBUT and Lissamine green staining in relation to treatment duration

Treatment duration (years)	Number of patients	TBUT (%)			Lissamine Green staining (%)		
		Normal	Mild-moderate	Severe	Normal	Mild-moderate	Severe
≤ 1	26	19 73.1%	7 26.9%	0 0%	25 96.2%	1 3.8%	0 0%
2–5	37	11 29.7%	26 70.3%	0 0%	30 81.1%	7 18.9%	0 0%
6-10	20	1 5%	19 95%	0 0%	5 25%	15 75%	0 0%
> 10	11	0 0%	7 63.6%	4 36.4%	0 0%	10 90.9%	1 9.1%

Table 6. Correlation between number of drugs and OSDI, Schirmer's test

Number of drugs	Number of patients	OSDI (%)			Schirmer's test (%)		
		Normal	Mild-moderate	Severe	Normal	Mild-moderate	Severe
1	42	16 38.1%	25 59.5%	1 2.4%	7 16.7%	23 54.8%	12 28.6%
2	37	7 18.9%	25 67.6%	5 13.5%	5 13.5%	12 32.4%	20 54%
3	13	3 23.1%	10 76.9%	0 0%	3 23.1%	9 69.2%	1 7.7%
4	2	0 0%	2 100%	0 0%	0 0%	0 0%	2 100%

Table 7. Correlation between number of drugs and TBUT, Lissamine green staining

Number of drugs	Number of patients	OSDI (%)			Schirmer's test (%)		
		Normal	Mild-moderate	Severe	Normal	Mild-moderate	Severe
1	42	21 38.1%	21 59.5%	0 2.4%	34 81%	8 19%	0 0%
2	37	7 18.9%	27 73%	3 8.1%	19 51.4%	17 45.9%	1 2.7%

Number of drugs	Number of patients	OSDI (%)			Schirmer's test (%)		
		Normal	Mild-moderate	Severe	Normal	Mild-moderate	Severe
3	13	3 23.1%	9 69.2%	1 7.7%	7 53.8%	6 46.2%	0 0%
4	2	0 0%	2 100%	0 0%	0 0%	2 100%	0 0%

Among controls, 42 (44.6%) patients had symptoms of OSD on the OSDI questionnaire. Of those, 40.4% had mild to moderate symptoms and 4.25% had severe symptoms. Schirmer's test showed 50 patients (53%) with decreased tear production. TBUT was abnormal in 45 patients (47.8%). Lissamine green staining was positive in 30 patients (31.8%) (Table 8).

Table 8. Test results of controls

Results	OSDI %	Schirmer's test %	TBUT %	Lissamine green staining %
Normal	55.3%	46.8%	52.1%	68.0%
Mild-moderate	40.4%	38.2%	36.1%	29.7%
Severe	4.2%	14.8%	11.7%	2.1%

Discussion

The ocular surface is one of the most complex tissues in the body as it is not protected by skin, which is the body's most valuable defence against both desiccation and infection. The stability of the ocular surface provides protection and a refractive surface that allows for good-quality vision. The tear film is fundamental in the maintenance of the ocular surface. Any condition that adversely affects the stability and function of the tear film may result in unstable tear film and OSD onset.

As defined by the International Dry Eye Workshop (DEWS),[6] dry eye is a multifactorial disease that results in:

1. symptoms of discomfort;
2. visual disturbance;
3. tear film instability;
4. potential damage to the ocular surface;
5. increased osmolarity of the tear film; and
6. inflammation of the ocular surface.

Dry eye disease is of two types: aqueous tear-deficient dry eye (ADDE) and evaporative dry eye (EDE).

OSD is a common comorbidity in patients with glaucoma due to the fact that its prevalence increases with age as in glaucoma. OSD is known to occur in approximately 15% of the general elderly population and is reported in 48% to 59% of patients treated with topical antiglaucoma medications.[1,7,8] One in six patients with glaucoma has OSD symptoms severe enough that they need some form of treatment for OSD.

The German Glaucoma and Dry Eye Register[9] reported that the incidence of dry eye increases with age and among women. We had a greater number of males in the study group. The severity of OSD among males and females was not statistically different. (Chi square test/ Fisher exact test p = 0.142). They reported increased prevalence of dry eye with long-term use of multiple topical antiglaucoma medications, a similar observation made in our study.

Barisic *et al.*[10] observed that 75% of patients had symptoms of OSD using the OSDI questionnaire. Of those, 17% had scores in accordance with mild OSD, 11% had moderate OSD, and 47% had severe OSD. The overall prevalence was similar to our study (72.4%). In our study, we had more patients with mild to moderate symptoms. However, they had more patients with severe symptoms (47%) when compared to our study (6.4%).

Vinutha *et al.*[11] observed that 32% of patients reported symptoms in at least one eye on the OSDI questionnaire, which was less when compared to our study. TBUT (74%) (mild to moderate: 54%; and severe: 20%) and Lissamine green staining (47%) results were more positive in their study when compared to our study. Schirmer's test showed more positive results in our study (total: 84%; mild to moderate: 46.8%; severe: 37.2%) when compared to their study (total: 72 %; mild to moderate: 50.5%; severe: 21.5%). They also reported that with increased treatment duration and number of medications more patients became symptomatic and test results became abnormal. Our observation was similar to their study.

Leung *et al.*[1] examined the prevalence of OSD using the OSDI questionnaire, TBUT, Lissamine green staining, and Schirmer's test. In their study, 60 patients (59%) had symptoms of OSD in the OSDI questionnaire, less than our study (72.4%). Twenty-seven patients (27%) had severe symptoms in their study, more than in our study. They observed that the use of more BAK-containing drops was significantly associated with higher prevalence of abnormal results on Lissamine green staining (22%). None of them had severe staining with Lissamine green. In our study, Lissamine green staining was positive in 34 patients (36.2%) and only one patient had severe staining. Similar to the findings by Leung *et al.*,[1] we found that with increased number of medications test results became more positive. We were not able to comment on the preservatives in the medication because of the

wide range of eye drops being sold by different pharmaceutical companies in our country.

Fechtner *et al.*[8] used the OSDI to describe the prevalence of OSD among patients treated for glaucoma and found that 48.4% of the patients had mild to severe symptoms, which was significantly less when compared to our study, where 72.4% patients had symptoms of OSD. Patients on one medication had a mean OSDI score of 12.9 ± 13.1, which was significantly lower when compared to patients on two (16.7 ± 17.0; P = 0.007) or three medications (19.4 ± 18.1; P = 0.0001). This was similar to our study, where with increased number of medications from one or two to three or four, the mean OSDI score increased from mild (19.6) to moderate (23.1), respectively, although it was not statistically significant (p = 0.183).

In a study published by Garcia-Feijoo *et al.*,[12] the overall prevalence rate of OSD was 59.2%, with 25.7% having mild symptoms, 13.2% with moderate symptoms, and 20.3% with severe symptoms on the OSDI questionnaire, which is lower compared to our study. Patients on treatment for less than six years had a significantly lower mean OSDI score (18: mild OSD) when compared to patients on treatment for six years or more (23: moderate OSD; P = 0.03). With increased number of medications from one or two medications to three or four medications, the mean OSDI score increased from mild to moderate, although the difference in scores was not statistically significant (P = 0.15). In our study, mean OSDI scores in patients using medications for less than five years was 16.5, indicating mild OSD, while in patients using medications for more than five years it was 27.1, indicating moderate OSD. This difference (p = 0.00) was statistically significant and correlated with their study.

The effect of preservatives in antiglaucoma medications on the ocular surface and their role in causation of OSD has been greatly investigated. However, we did not study the preservatives in the medications used by the study group.

The differences among the prevalence of OSD in different studies could be due to differences in methodology, severity of disease, age, duration of therapy, and the type and number of medications used. The severity of dry eye was more evident with TBUT and Schirmer's test as compared to Lissamine green staining.

In the studies mentioned above, only Leung *et al.* and Vinutha *et al.* used methods such as the OSDI questionnaire for subjective analysis, Schirmer's test for tear production, TBUT for Meibomian gland function, and Lissamine green surface staining to asses OSD. In our study, we also used all the methods to assess OSD and compared it with the age-matched controls. This helped us to assess them along with glaucoma patients, helping to compare the effect of glaucoma medications in the occurrence of OSD.

Conclusion

From our study, we conclude that almost 75% of the patients with glaucoma experienced some level of OSD. OSD was more common in patients using IOP-lowering drugs than controls, indicating that antiglaucoma medications contribute to its occurrence. There was a statistically significant correlation between increased treatment duration and worsening of OSD symptoms. Further, with increased number of topical medications, there was a clinically relevant increase in OSD symptom severity. Finally, OSD can influence treatment adherence and success, thus greatly influencing the quality of life of the glaucoma patients though we did not study this aspect of glaucoma medications. Educating patients about adverse effects of drugs and recommending them to avoid environmental circumstances such as dry air and long working hours in front of the computer play a crucial role in glaucoma management. Patients may enjoy a healthier ocular surface and better quality of life by switching over to medications with a smaller percentage of BAK or BAK-free.

Further studies that compare the effects of BAK and BAK-free agents on OSD are needed to validate the beneficial influence of BAK-free agents.

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Case series of cultivated oral mucosa epithelium transplantation for limbal stem cell failure: experience in Malaysia

Kah Lay Oh[1], Aida Zahidin[1], Umi Kalthum Md Noh[1], Safinaz Mohd Khialdin[1], Ghee Chien Ooi[2], Kong Yong Then[3]

[1]Department of Ophthalmology, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia; [2]CryoCord Sdn. Bhd., Malaysia;[3] International Specialist Eye Centre, Kuala Lumpur, Malaysia

Abstract

Purpose: *To report a case series of seven eyes (six patients) with severe limbal stem cell failure who underwent cultivated oral mucosa epithelium transplantation (COMET) in preparation for corneal transplant surgery and assess the change in visual acuity postoperatively.*

Design: *Case series.*

Methods: *A retrospective analysis of an interventional case series of six patients with severe limbal stem cell deficiency who underwent COMET between 2012 and 2015 was performed. Six eyes had COMET followed by corneal transplant, and one eye had corneal transplant preceding COMET. The change in the visual acuity after operation was evaluated.*

Results: *A total of six patients with seven eyes were studied. All of them had severe ocular surface disease with limbal stem cell deficiency (LSCD) secondary to chemical injury (five eyes), SJS (one eye), and severe ocular rosacea (one eye). Four eyes had improvements in visual acuity, two of which achieved best corrected visual acuity (BCVA) of 6/12.*

Conclusion: *The use of COMET helps to optimize the ocular surface in severe LSCD for further corneal transplant surgeries. It has helped to improve the graft uptake and subsequent visual improvement, especially in chronic chemical burn cases.*

Keywords*: acne rosacea, chemical injury, corneal transplant, cultivated oral mucosa epithelial transplantation (COMET), Stevens-Johnson syndrome (SJS)*

Introduction

Limbal stem cells are essential for maintaining the transparency and clarity of the cornea, as these cells are self-regenerating and allow renewal of the corneal

Correspondence: Dr. Safinaz Mohd Khialdin, Department of Ophthalmology, 9th Floor, Clinical Block, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latiff, 56000 Cheras, Kuala Lumpur, Malaysia.
E-mail: drsafinaz_1978@yahoo.com.my

epithelium. They are thought to reside at the basal layers of the corneal epithelium and limbus.

When limbal stem cells are damaged, there will be migration of conjunctiva epithelial cells to the ocular surface, hence causing neovascularization and loss of corneal clarity. The causes of LSCD can be generally divided into primary or congenital, such as aniridia and ectodermal dysplasia, and secondary or acquired, such as chemical injury, Stevens-Johnson syndrome (SJS), and ocular cicatricial pemphigoid.[1] We report six cases of clinically evident severe LSCD who underwent cultivated oral mucosa epithelium transplantation COMET: four cases of chemical injury, one case of SJS, and one of acne rosacea, respectively. Their best corrected postoperative visual acuity was evaluated.

Case reports

Case 1

A 46-year-old healthy Malay man presented with history of severe acid injury to both eyes ten years ago. He was completely blind in the right eye and had counting finger vision in the left eye. Examination revealed bilateral symblepharon and almost total corneal vascularisation with pannus. There was poor cornea wettabilty in both his eyes. He underwent staged procedure of left eye COMET, followed by deep anterior lamellar keratoplasty (DALK) four months later (Fig.1). At three months following corneal transplant, the best corrected visual acuity (BCVA) had improved tremendously to 6/15. He developed cataract a year later, which brought down his vision to counting finger. After a successful cataract surgery and intraocular lens implant, he achieved 6/12 vision in the left eye. He was followed up for a duration of four years.

Case 2

A 37-year-old healthy Chinese man presented with poor vision in his left eye after chemical injury to the affected eye one year earlier. On presentation, vision in the left eye was hand movement and right eye vision was 6/6. Examination revealed inferior symblepharon with total corneal scarring and vascularisation of the left eye. There were poor details of anterior segment and beyond. He underwent left eye COMET followed by an uneventful penetrating keratoplasty (PK) with amniotic membrane transplantation (AMT) five months post COMET (Fig. 2). Postoperatively, his left BCVA improved significantly to 6/12 at ten months post PK with no evidence of graft rejection. His follow-up duration was one year.

Case 3

A 44-year-old healthy Chinese man presented with right eye poor vision following one-month history of acid splash to his right eye. On examination, the visual acuity

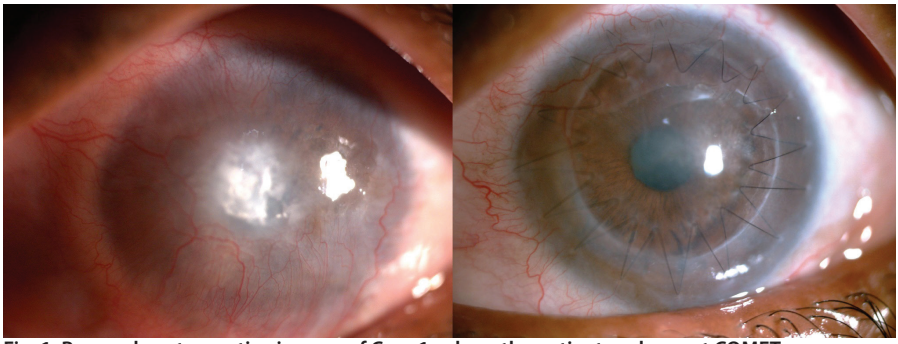

Fig. 1. Pre- and postoperative images of Case 1, where the patient underwent COMET followed by DALK. There was an improvement in corneal clarity.

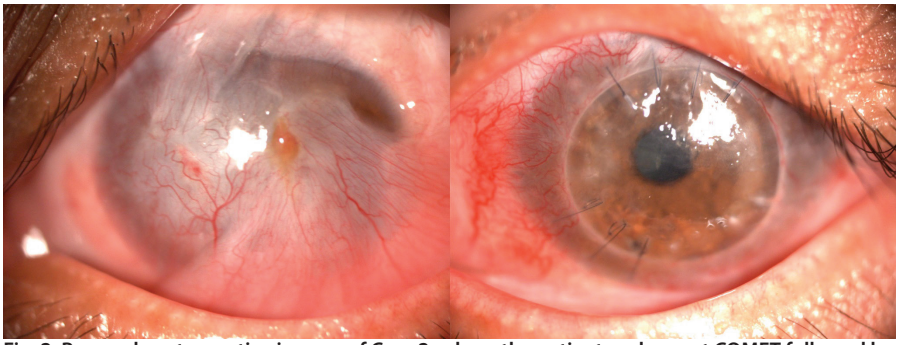

Fig. 2. Pre- and postoperative images of Case 2, where the patient underwent COMET followed by PK. The central cornea button remained clear with no evidence of rejection.

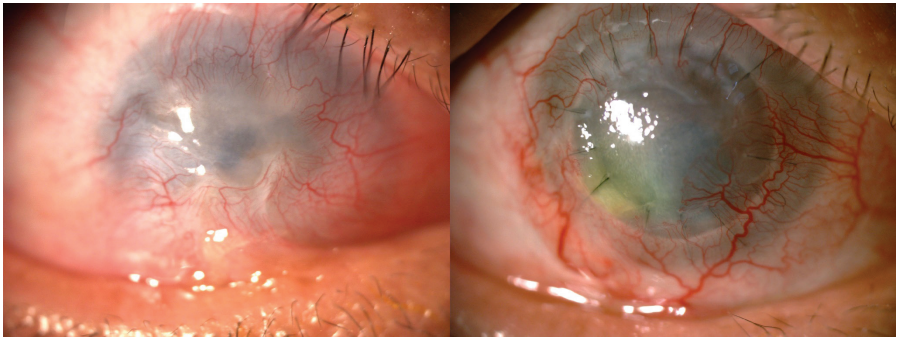

Fig.3. Pre- and postoperative images of Case 3, where the patient underwent COMET followed by PK. There was presence of vascularisation and a small persistent epithelial defect.

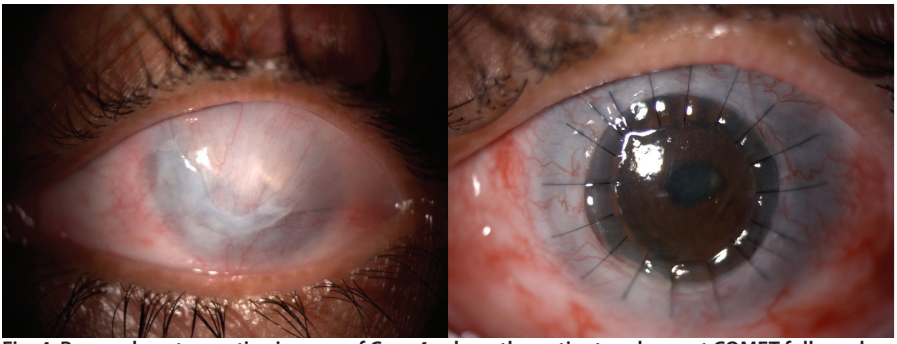

Fig. 4. Pre- and postoperative images of Case 4, where the patient underwent COMET followed by PK. There was an improvement in corneal clarity and ocular surface.

in his right eye was counting fingers. Ocular examination revealed right inferior symblepharon with total cornea epithelial defect and severe limbal ischaemia. One year post injury, he underwent right eye COMET, followed by PK with cataract extraction and intraocular lens implantation seven months post COMET (Fig. 3). Visual acuity at three-months postoperatively was hand movement with failed corneal epithelial healing. At five months post PK, he developed acute graft rejection which was treated with intensive steroids. However, his vision did not improve much and remained at counting fingers at three feet. During the last review, there was presence of heavy vascularisation and a small persistent epithelial defect of the cornea. His follow-up duration was 4 years.

Case 4

A 44-year-old healthy Malay man presented with long standing bilateral poor vision. He sustained chemical injury to both eyes with liquid ammonia 20 years ago. His vision was hand movement bilaterally. Ocular examination showed total limbal stem cell failure bilaterally and densely opaque cornea with 360° vascularisation. There was loss of iris details. However, there was good and stable tear film property in both his eyes. He underwent left eye COMET in November 2014 and PK with AMT five months post COMET (Fig. 4). His postoperative visual acuity improved to 6/36. This was attributed to the presence of persistent epithelial defect. However, his vision dropped further due to cataract formation and presence of corneal vascularisation. He was under follow-up for a period of two years.

Case 5

A 58-year-old Chinese female presented with progressive poor vision in both eyes for one-year duration. She always had problem with recurrent facial acne, but never sought medical attention for this problem. Her visual acuity at presentation was 6/60 OD and counting finger OS. Ocular examination showed bilateral severe

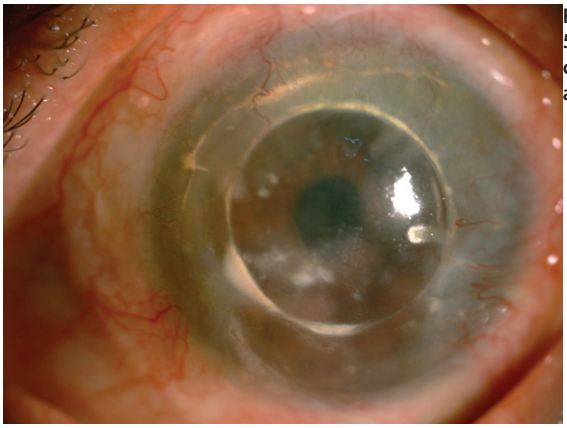

Fig. 5. Postoperative image of Case 5 showing clinical improvement in cornea epitheliopathy after DALK and COMET.

corneal scarring with poor cornea wettability and eyelid telangiectasia. There were bilateral sectoral symblepharon and vascularisation on the superior cornea. A diagnosis of ocular rosacea was given. Her right eye's condition improved after a conjunctival epitheliectomy and her right BCVA improved to 6/9.5. She underwent left eye uneventful superficial keratectomy followed by DALK with AMT five months later. Postoperatively, she developed total LSCD with vision of 6/60. In view of the total LSCD, she had COMET done one year after her DALK (Fig. 5). Unfortunately, her left vision remained at counting fingers due to cornea vascularisation with scarring. During her last ocular examination, there was improvement in the tear film with clinical improvement in cornea epitheliopathy. Her follow-up duration was seven years.

Case 6

A 59-year-old Chinese man presented with left poor vision for two years. He had history of SJS with ocular involvements secondary to gout medications.

Visual acuity was 6/9 OD and hand motion OS. Ocular examination showed superior symblepharon with loss of limbal stem cell superiorly of the right eye. A similar but denser symblepharon with total loss of limbal stem cells and significant scarring was noted in the left eye. He came back two years later with profound drop in vision to counting fingers in his right eye. Left vision was perception to light. He underwent uneventful bilateral COMET (Fig. 6). However, his BCVA was not much improved, due to presence of bilateral significant vascularisation and left cornea scarring. A second bilateral COMET was performed one year after the first surgery. Unfortunately, his vision did not improve much, with BCVA of hand movement, as both corneas remained hazy with presence of vascularisation. He was not keen on further corneal transplants. His follow-up duration was five years.

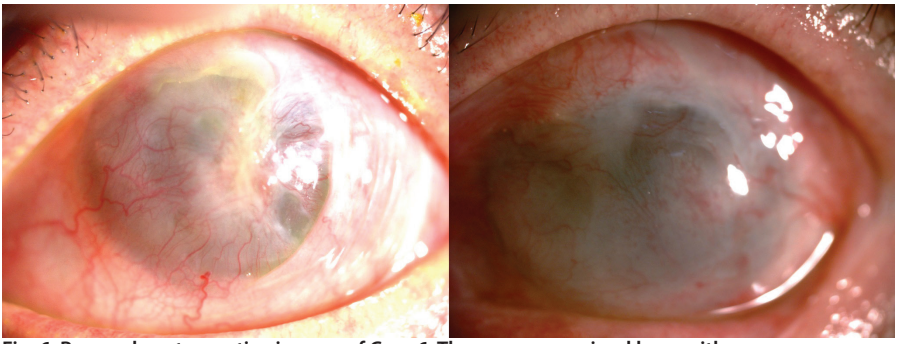

Fig. 6. Pre- and postoperative images of Case 6. The cornea remained hazy with presence of vascularisation despite undergoing COMET twice.

Cultivation of oral mucosal epithelial cells transplantation with amniotic membrane-based sheets procedure

The stages involved in COMET include harvesting and cultivating the buccal mucosa on the amniotic membrane (AM), followed by transplantation of the cells.

The buccal mucosa biopsy was obtained with the patients' consent. The buccal mucosa was sterilized and a 5 mm diameter tissue was collected. The tissue was then packed and transported under room temperature to the laboratory.

All cell preparation was done in a Current Good Manufacturing Practice (cGMP) accredited laboratory. The collected sample was placed on top of an AM which served as a base for the buccal mucosa culture. These cells were moistened with Defined Keratinocyte-Serum-Free Medium (SFM) (Gibco). Next, 100 U/ml of penicillin,100 µg/ml of streptomycin, and 0.25 µg/ml of amphotericin were added. The cells were incubated in 5% CO2 incubator at 37°C for about six to eight weeks.

Once the cells had reached confluency and covered the entire surface area of the AM, they were transported back to the transplantation site under room temperature. Before they were transplanted onto the patient's eye, they were taken for bacterial and fungal infection testing. The last stage was either a standard procedure of LK or PK.

Discussion

LSCD is a condition where the limbal stem cells are unable to regenerate to protect the corneal epithelium.[2,3] It remains a challenge to treat LSCD as there is absence of limbal stem cells to ensure proper epithelial healing and integrity of the ocular surface. Limbal stem cells can be either autografts, allografts, or cadaveric.[4,5] Treatment of unilateral LSCD may include limbal autografts, cultivated limbal epithelial transplantation (CLET), or simple limbal epithelial transplantation (SLET) from the

healthy fellow eye. However, CLET is dependent on cultivation conditions and does not show promising results in eyes with bilateral ocular surface abnormalities, such as SJS.[4] SLET is a novel and easy procedure of transplanting a strip of healthy limbal tissue using an AM. As this technique requires less donor tissue and does not need a laboratory for cell expansion, it is a simple yet effective method in treating unilateral LSCD.[6]

In bilateral cases, the option of allograft limbal transplant from a cadaver, a family member, or COMET may be considered.[7,8] By cultivating the patient's own oral mucosal epithelial cells and transplanting onto the diseased ocular surface, COMET is believed to show promising results.[8-10] The study by Nishida *et al.* suggested that COMET may be effective to restore the ocular surface and restore vision in patients with bilateral LSCD.[8] The advantages of COMET are the suitability for patients with bilateral LSCD and lack of long-term use of immunosuppresants.[9] Several studies have shown that COMET combined with PK may improve graft survival and corneal clarity.[11] In this study, COMET was the mainstay of treatment for patients with bilateral LCSD.

In the present case series, all the patients were followed up for more than one year. Half of them had an improvement in BCVA, with two eyes obtaining 6/12 vision. In these cases, the LSCD cases were secondary to chemical injury. The improvement in vision was stable throughout the four-year follow up. The pathophysiological events that may influence the final outcome of the vision in chemical injury depend on the severity of the limbal stem cell injury and the extent of penetration of the chemical intraocularly.[12] We believe that this group fared comparatively better as the insult was a one-off event which did not lead to ongoing inflammation. The six cases are summarized in Table 1.

Table 1. A summary of case series of COMET

Case	Initial Vision	Final Vision	Indication	Type of Surgery	Reason of poor vision (if any)	Follow-up duration
1	CF	6/12	Chemical injury	COMET + DALK	nil	4 years
2	HM	6/12	Chemical injury	COMET + PK	nil	1 year
3	CF	CF	Chemical injury	COMET + PK	Acute graft rejection	4 years
4	HM	6/36	Chemical injury	COMET + PK	Persistent epithelial defect	2 years

Case	Initial Vision	Final Vision	Indication	Type of Surgery	Reason of poor vision (if any)	Follow-up duration
5	CF	6/60	Ocular rosacea	DALK + COMET	Cornea vascularization with scarring	7 years
6	RV: CF LV: PL	RV: HM LV: HM	Stevens-Johnson syndrome	COMET twice	Failed COMET	5 years

We observed patients with SJS did worse than those with chemical injury, as evidenced by persistent extensive vascularisation and scarring after COMET. Previous studies also showed similar findings.[13-15] It is likely that SJS eyes have a poorer preoperative ocular surface, poor tear function, and metaplasia of the conjunctival epithelium as well as lid margin abnormalities and keratinisation.

We also noted that surgical success depends on the severity and chronicity of the disease. In the group of patients with chemical injury, the outcome of surgery in Case 4 was the worst as it started with a Grade 4 chemical injury of 20 years of duration. We believe that the chronicity of the disease leads to total loss of limbal and corneal epithelium. In his eye, there was epithelization of the cornea by the conjunctival epithelium. The clinical features of LSCD chronicity include severe pannus formation and cornea vascularisation, which was present in his eyes. Corneal vascularisation and low-grade inflammation are the key factors in determining corneal graft survival. Although COMET helped reduce the amount of corneal vascularity, it did not totally eliminate the presence of active vessels.

Most patients in our series managed to achieve navigational vision following their surgery. They reported independence in daily tasks, which helped to boost their confidence and improve family relationships through facial recognition. Therefore, COMET has been shown to improve the ocular surface in patients with secondary LSCD, as this procedure reduces corneal scarring and vascularity. In particular, it appears to improve corneal transplant outcomes in patients with ocular chemical injury in our series. The final visual improvement is largely affected by the degree of initial insult and severity of ocular surface disease. Careful patient selection and proper counselling is of utmost importance to ensure realistic expectations to the outcome of surgery.

Acknowledgements/Disclosure

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Bloody tears: a case of bilateral ulcerative blepharitis

Praveena Gupta[1], Laura Di Meglio[1], Ashley Behrens[1]
[1]Wilmer Eye Institute, Johns Hopkins University, Baltimore, Maryland, USA

Abstract
Chronic blepharitis leading to bilateral ulceration is rare to encounter. A 49-year-old African American female presents with bloody tears, severe pain, and photophobia in both eyes. Clinical presentation called for ulceration on the upper lid margins with excavated wound which bled on gentle rubbing. A systemic health review in combination of the symptoms and clinical picture led to the diagnosis of severe ulcerative blepharitis. Immediate oral antibiotics were started along with topical antibiotic cream. Ulcerative blepharitis can be easily misdiagnosed with sebaceous cell carcinoma. The pathophysiology of ulcerative blepharitis points to synergy between infectious entity and inflammatory aetiology, with either bacterial or fungal microorganisms as the trigger agents. Almost all cases of ulcerative blepharitis should include a dermatological evaluation given there is a strong association between ulcerative blepharitis and atopic dermatitis.

Keywords*: atopic dermatitis, blepharitis, ulcerative blepharitis*

Introduction

Blepharitis is a very common condition encountered in our daily clinic. However, ulcerative blepharitis can be a clinical dilemma to diagnose and treat. Typically, blepharitis involves both inflammatory and infectious entities. The most common infectious agent for causing blepharitis is Staphylococcus Sp. However, many other common species have also been isolated in recent years.[1,2] In a clinical setting of ulcerative blepharitis, one has to evaluate the dermatological status of the patient. Almost all cases of ulcerative blepharitis are associated with atopic dermatitis.[3] A close clinical resemblance of lid margin ulceration with sebaceous cell carcinoma should not be neglected. In cases where systemic oral antibiotics fail to contain the disease, a biopsy is warranted.

Case report

49-year-old African American female presents with mucousy bloody tears, severe pain, and photophobia in both eyes. Other symptoms included itchiness and burning sensation on the eye lids for more than a month. Her medical history is

Correspondence: Praveena Gupta, 600 N Wolfe Street, Wilmer Eye Institute, Johns Hopkins University, Baltimore, Maryland 21287, USA.
E-mail: pgupta26@jhmi.edu

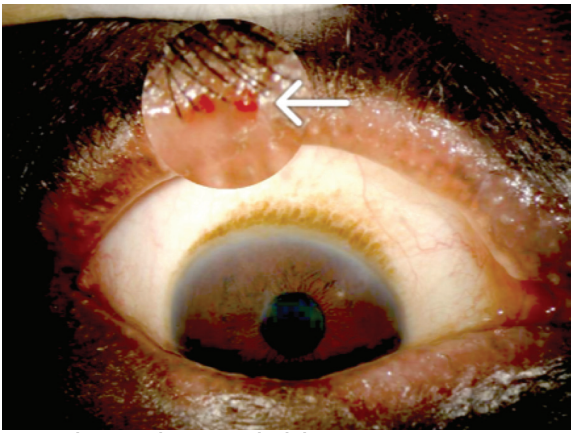

Fig. 1. Ulcerative lesions at the lid margins.

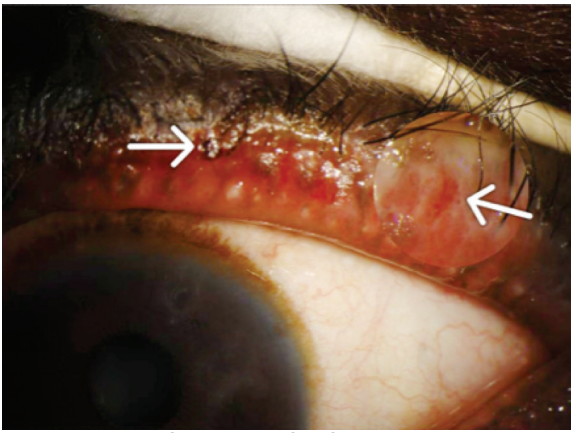

Fig. 2. Hypervascularisation at the ulceration site.

positive for hysterectomy, asthma, hypertension, and several flare up episodes of atopic dermatitis. On examination she was 20/25 OD and OS with very slow reading on Snellen acuity. Her pupils, confrontation field, and muscle motility were unremarkable. Intraocular pressure was measured 17 mmHg in the right eye and 17 mmHg in the left eye using iCare. Slit lamp exam revealed severe excavated wounds that were bleeding on both upper lid margins and a few erosive ulcerations on the lower lids (Figs. 1 and 2).

The eyelash bases were loaded with greasy scales that were thickened and hard. Needless to say, conjunctiva in both eyes were injected (Fig. 3) and the palpebral conjunctiva had mucous strands with inflamed papillae. There were areas of

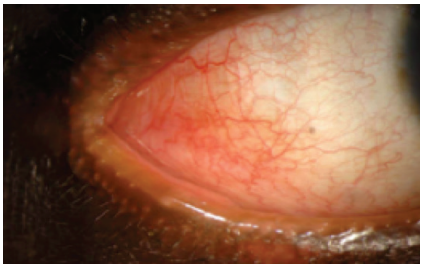

Fig. 3. Conjunctival injection and inflamed papillae.

thinned eye lashes and several collarettes with loose epithelial scales bilaterally. Trace nuclear sclerotic cataracts was noted and the posterior segment exam was unremarkable.

Discussion

Clinically, blepharitis can be categorized under Staphylococcic blepharitis, seborrheic blepharitis, and mixed forms of primary blepharitis.[4] These can be further classified into anterior and posterior blepharitis, where anterior affects the anterior lid margins and eyelash base, and posterior involves the posterior lid margin, commonly associated with abnormalities of the Meibomian glands. In most cases, patients are diagnosed with a mix of both anterior and posterior blepharitis, and present with chronic inflammation of the lid margins.[5] The presentation of our patient was ulcerative blepharitis, perhaps as a consequence of long-term untreated seborrheic infection. Importantly, our patient had two recent episodes of flare up of atopic dermatitis and was treated with oral and topical antibiotic combinations.

Most patients with ulcerative blepharitis present with a history of severe atopic dermatitis, which includes symptoms of long standing dry itchy skin, asthma, and allergic rhinitis. It is very important to take a detailed history of the patient, as these findings can be crucial in diagnosing and treating this condition. In the absence of these co-morbidities, the differential diagnosis of sebaceous cell carcinoma needs to be strongly considered. Our patient had a positive history and recent flares of atopic dermatitis that helped lead to her diagnosis and consequent treatment. Atopic dermatitis was diagnosed in almost all of the patients that presented with severe ulcerative blepharitis in a study conducted on 407 consecutive cases of chronic bilateral blepharitis. *Candida* species predominantly infected atopic patients with ulcerative lid margins.[3,6,9] Atopic patients exhibit a defect in their cell-mediated immunity and possibly also a defective IgA antibody response. These immunological changes may contribute to the development of a localised inflammation of the lids that is initiated by a variety of microorganisms.[6] Sporadic case reports have also surfaced on the involvement of *herpes simplex* in erosive ulcerative blepharitis, and underlying eczema can be a predisposing risk factor.[7,8] Therefore, cultures from the lids and lashes for fungal or herpetic aetiology should not be ruled out when there is no noted improvement after

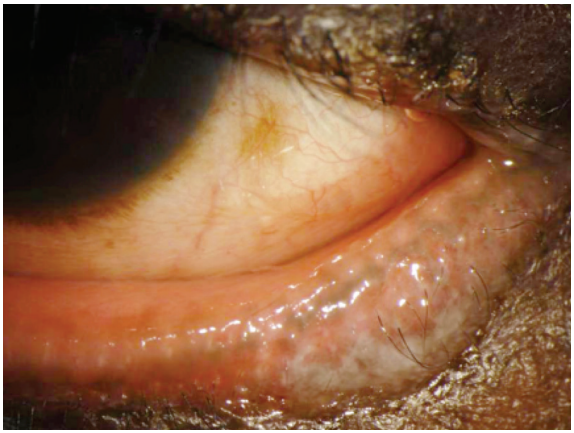

Fig. 4. Loose epithelial scaling and lid thickening, thinned lashes with mucous discharge.

compliant treatment.

The distinguishing sign of seborrheic blepharitis is the combination of yellowish, greasy scales that loosely attach to the base of the follicles (Fig. 4). Without treatment, chronic seborrheic blepharitis can evolve into ulcerative blepharitis, which is characterized by hard, thickened, and matted crusts along the base of the cilia and lid margins that can result in bleeding. The transformation into ulcerative blepharitis can typically be prevented with treatment of the underlying seborrheic blepharitis. However, the simple treatment relies on patient compliance and long-term commitment. A frank and healthy discussion with the patient is the crucial first step, where we educate on the importance of keeping the lids and lashes clean using hypoallergenic baby shampoo or lid scrub. In uncontrolled cases, a topical antibiotic is recommended; however, one has to be mindful that long-term use and abuse of topical antibiotics can result in resistant bacteria.[5] Our patient improved on an oral dose of doxycycline for ten days with antibiotic ointment twice daily with extensive lid hygiene.

Conclusion

Ulcerative blepharitis is a clinical challenge to diagnose and treat effectively. The causative agents can be bacterial, fungal, or viral, thus making it difficult to initiate a treatment. However, there are certain tell-tale signs that can provide clues to the correct diagnosis. The presence of hardened matted crusts with dry thick scales of dry skin attached to the base of cilia can give away signs for quick management. One should consider culturing the specimens in cases of recalcitrant blepharitis. Also, a consultation with a dermatologist is highly recommended for patients who present with ulcerative blepharitis due to its strong association with atopic dermatitis.

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Safety and efficacy of posterior iris claw intraocular lens fixation in aphakic patients

Rosemary Tomy[1], Rajkumar Maheshwari[1], Ansa Parveen Kunhu Muhammed[2], Venkataramana Kalikivayi[2], Sajeev Cherian Jacob[1]
[1]Consultant Ophthalmologist, Ahalia Foundation Eye Hospital, Palakkad, Kerala, India; [2]Ahalia School of Optometry, Palakkad, Kerala, India

Abstract

Purpose: *To assess the indications and visual outcome of eyes undergoing posterior iris fixated intraocular lens (IFIOL) implantation for aphakia, to identify reasons for poor visual outcome, and report occurrence of complications.*

Methods: *In this retrospective case series study, all cases of posterior IFIOL fixation performed over a 30-month period were identified retrospectively. Preoperative and postoperative evaluations comprised objective and subjective refraction, best corrected visual acuity (BCVA), slit lamp biomicroscopy, applanation tonometry, and dilated fundus examination.*

Results: *Fifty-six eyes of 56 patients were analyzed. Mean age was 60.55 ± 17.2 years. The most common indication for IFIOL implantation was surgical aphakia following complicated cataract surgery (n = 33; 58.9%) followed by trauma (n = 10; 17.9%), dropped nucleus/IOL during primary surgery (n = 6; 10.7%), and subluxated/dislocated lens-induced glaucomas (n = 5; 8.9%). BCVA better than or equal to their preoperative BCVA was achieved in 96.43% patients. The surgical aphakia and paediatric/adolescent groups had the best visual results while the dropped nucleus/IOL group and subluxated lens-induced glaucoma groups fared poorly. On the long-term follow-up visit, the most common complication noted was pigment dusting on the corneal endothelium (65.7%).*

Conclusion: *The long-term results suggest that posterior IFIOL implantation is a safe and effective method for correction of aphakia and can be used for a wide range of indications in eyes without adequate capsule support. It may be considered an easier and faster alternative with minimal manipulation to anterior segment structures in paediatric and post-traumatic aphakic eyes.*

Keywords*: iris claw, intraocular lens (IOL), aphakia*

Introduction

In aphakic eyes without adequate capsular support for intracapsular or posterior chamber sulcus placement of intraocular lens (IOL), alternative methods of IOL fixation are to be considered. This presents a debate between selection of anterior

Correspondence: Dr. Venkataramana Kalikivayi, Head of the Department, Ahalia School of Optometry, Palakkad, Kerala, India.
E-mail: kalikivayi@yahoo.com

chamber IOL (ACIOL), scleral-fixated IOL (SFIOL), and iris-fixated IOL (IFIOL).[1,2]

Primary and secondary implantation of angle supported ACIOLs have reported endothelial cell loss, pseudophakic bullous keratopathy (PBK), uveitis–glaucoma–hyphaema syndrome, and chronic cystoid macular edema (CME). Surgical risks with scleral-sutured SFIOLs include uveal/choroidal bleeding, damage to the blood–aqueous barrier in the ciliary body due to mechanical pressure of the haptics, chronic inflammation, CME, and a longer surgical time with more intraocular manipulation in comparison to ACIOL implantation. Furthermore, the transscleral sutures can lead to conjunctival erosions, scleromalacia, and endophthalmitis.[3,4]

Retro-fixated iris claw lens circumvents the aforesaid problems. The implantation of the IFIOL behind the iris better preserves the anatomy of the anterior segment with respect to the iridocorneal angle. The suture less technique lends to operating ease and avoids suture related complications. Its disadvantages may be iris chaffing and requirement of sufficient iris tissue.[5-7]

As there are only few works related to iris claw reported earlier, this work is planned to assess the indications and visual outcome of eyes undergoing IFIOL implantation for aphakia, to identify reasons for poor visual outcome, and report occurrence of complications.

Materials and methods

All cases of posterior IFIOL fixation performed by a single surgeon over a 30-month period were retrospectively identified. Preoperative data collected included demographics and aetiology of aphakia. Preoperative and postoperative evaluations comprised objective and subjective refraction, slit lamp biomicroscopy, applanation tonometry, and dilated fundus examination. The IOL power was calculated by the SRK-T formula using an A constant of 117.2. Fifty-six patients identified from the operating theatre logbook were called to the hospital for a long-term follow-up evaluation on May 2014. In addition to the clinical examination, optical coherence tomography (CIRRUS HD-OCT Model 400 - Spectral Domain; Carl Zeiss) was also done to evaluate retinal morphology and macular thickness. Visual acuity was converted to Log MAR for statistical ease and analysis was done using Microsoft Excel.

The IFIOL used was Model No. PIC 5580/PIC 5590 from Excel Optics (Chennai, India). It is a single piece biconvex PMMA IOL with an overall length of 8.00/9.00 mm and optic diameter of 5.50 mm. The haptics have fine fissures to capture a fold of midperipheral iris stroma through enclavation, where the iris is virtually immobile, less vascularized, and less reactive.[10] This makes the IFIOL independent of anterior segment size and conducive to pupillary dilatation.

IFIOL implantations were done under peribulbar anaesthesia except for the

paediatric patients, who were given general anaesthesia. IFIOL implantation was done as a secondary procedure in the surgical aphakia and trauma groups. The subluxated/dislocated lens induced-glaucoma group underwent pars plana lensectomy + trabeculectomy along with IFIOL implantation. The group in which nucleus/IOL was dropped during primary surgery underwent parsplana vitrectomy + phacofragmentation/ IOL explantation along with IFIOL implantation.

The surgical technique performed for all the patients started with separation of the conjunctiva from adhesions to expose the temporal or superior scleral tunnel of the primary surgery, later opened with an iris repositor. In the absence of a scleral tunnel, a 6 mm scleral tunnel was made at 12 o'clock. Anterior chamber (AC) was formed with viscoelastic and, if vitreous was noted, automated anterior vitrectomy was performed. Two corneal paracenteses were made diagonally opposite to each other at 3 and 9 o'clock in case of a superior tunnel. The IFIOL was inserted through the corneoscleral tunnel along its long axis and, once in the AC, was rotated such that the haptics were in line with the side ports. Holding the optic of the lens with a lens forceps, one haptic was pushed under the iris and lifted up to create a mild indentation on the iris. Simultaneously, a Sinskey hook was passed through the paracentesis on the same side and the midperipheral iris was enclavated between the claw haptics by applying gentle pressure. End point was noting the dimple at the site of enclavation. Similarly, haptic enclavation on the other side was done. Viscoelastic was then washed out and corneal paracenteses were hydrated. No iridectomy was performed. Postoperatively, topical steroids and antibiotics in a tapering schedule over six weeks were prescribed.

Results

The data of 56 patients were retrieved from the medical records department of our eye hospital and analysed for 56 eyes that underwent IFIOL. The study group consisted of 33 males and 23 females. The mean age was 59.4 ± 17.99 years, with a minimum age range of 1 to 83 years.

IFIOL was implanted most commoly in surgical aphakia following complicated cataract surgery (n = 33; 58.9%). The other etiological factors of aphakic patients who underwent IFIOL are given in Table 1.

Table 1. Aetiology of aphakia

S.no	Indication for iris claw lens	Number	Percentage
1	Complicated cataract surgery	33	58.9
2	Penetrating eye injury	10	17.9
3	ACIOL complications	2	3.6

S.no	Indication for iris claw lens	Number	Percentage
4	Dropped IOL during primary surgery	2	3.6
5	Dropped nucleus during primary surgery	4	7.1
6	Subluxated lens-induced glaucoma	5	8.9
	Total		56

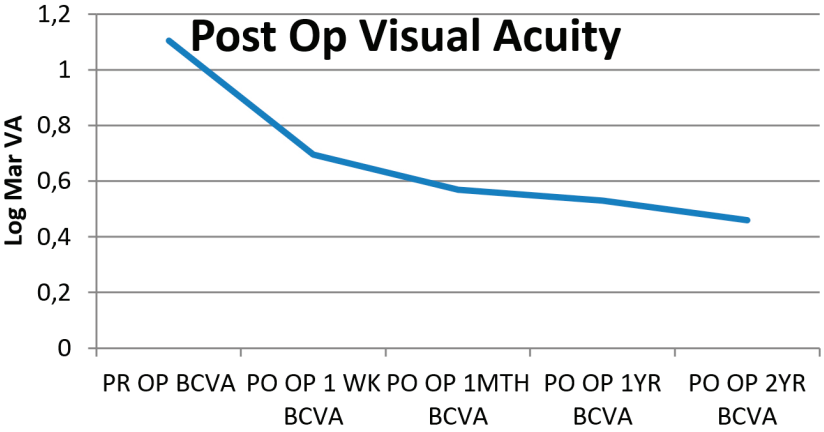

Fig 1. Pre- and postoperative Log MAR visual acuity.

The best corrected visual acuity (BCVA) preoperatively was found to be 1.10, which was improved to 0.69, 0.57, 0.53, and 0.46 Log MAR for postoperative one week, one month, one year, and two years, respectively, as shown in Figure 1. A paired t-test was performed between the preoperative BCVA and postoperative BCVA, which revealed a statistically significant p value less than 0.05 for all follow-up visits of one week, one month, one year, and two years.

At one-month follow-up, 66.6% patients achieved BCVA ≥ 6/12 and 83.3% achieved BCVA ≥ 6/18. Of the 33.3% patients whose BCVA < 6/12, the causes for decreased vision and co-morbidities are outlined in Table 2. There are two cases where postoperative visual acuity was reduced. The reason for the first case was due to macular puckering following pan retinal photocoagulation for proliferative diabetic retinopathy. The reason for the second case is due to the complications related to retinal detachment.

Table 2. Ocular comorbidity in BCVA < 6/12

Comorbidity	No. of Cases
Corneal pathology	2
Retinal pathology	11
Glaucomatous optic atrophy	3

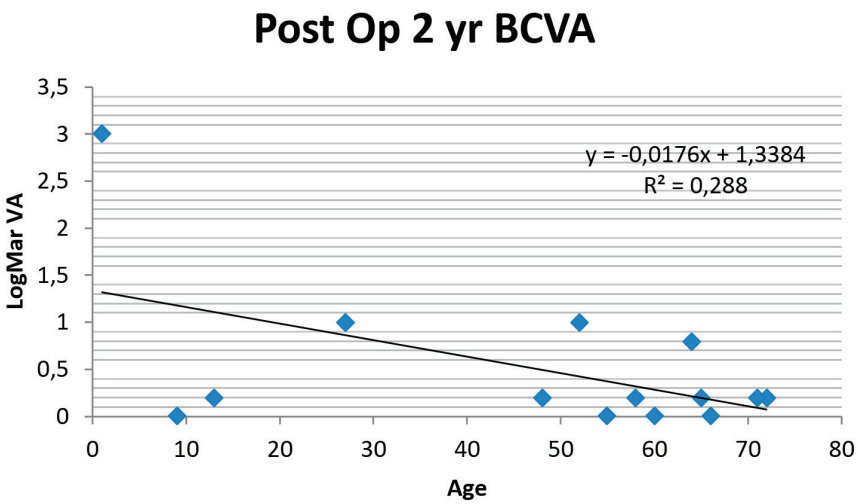

Fig 2. Correlation of age and Log Mar VA for a 2-year postoperative visit.

Pearson's correlation test was used to compare age with best corrected Log MAR visual acuity, which revealed positive correlations with one-week, one-month, and one-year follow-up with no statistical significance. However, it showed a negative correlation for a two-year follow-up with statistical significance of $p < 0.05$, shown in Figure 2.

Subjective refraction, intraocular pressure (IOP), and astigmatism data was also recorded for all patients in a follow-up visit to the hospital. The mean preoperative IOP was found to be 15.97 and postoperative IOP was found to be 14.72. A paired t-test was performed and revealed no statistical significance between pre- and postoperative visits in IOP. The mean preoperative and postoperative spherical equivalents were found to be + 8.25 D and -0.41 D, respectively, which revealed a statistically significant difference with $p < 0.05$. Keratometry readings for corneal curvatures were also recorded for pre- and postoperative visits. The difference in corneal curvature between both meridians was taken as astigmatism. The mean pre- and postoperative astigmatism was found to be 0.99 D and 1.89 D, respectively, and was found to be statistically significant with $p = 0.03$. This indicates

there is a significant increase in postoperative corneal astigmatism after IFIOL surgery.

On slit lamp examination, all the eyes were quiet and all the IFIOLs except one were well centred. The inferiorly decentred IOL was reclipped. Another patient had developed disenclavation four months postoperatively, which had been reclipped and was well centred on long-term follow-up. The most common complication noted was mild pigment dusting on the corneal endothelium in 65.7% of cases, followed by slight temporal ovalisation of the pupil/irregularities in 40%, more so in the penetrating corneoscleral injury trauma cases. Focal iris atrophy at the enclavation points/diffuse iris atrophy were noted in 40%. The entire postoperative complication rates are given in Table 3.

Table 3. List of complications on long-term follow-up for > 1 year

S.No	Complications	Number	Percentage
1	Pigments on endothelium	23	65.71
2	Pupil ovalisation/irregularities	14	40
3	Focal/diffuse iris atrophy	14	40
4	IOL decentration	2	5.7

On OCT, the mean Central Macular Thickness was 287.37 µ. Three patients had CME, one each in the IOL explantation, trauma, and surgical aphakia groups. Five patients had epiretinal membrane, of which two were post pars plana vitrectomy/IOL explantation/silicone oil implant/endolaser for IOL/nucleus drop with RD, one was post panretinal photocoagulation for proliferative diabetic retinopathy, one post focal laser for clinically significant macular edema, and one was idiopathic. The visual outcome was analysed with respect to the aetiology of aphakia subgroups, as given in Table 4. The surgical aphakia and paediatric groups had the best visual results. One patient (1.8%) required a re-operation for IOL decentration, in which IFIOL was reclipped after three months of initial treatment.

Table 4. Subgroup analysis of visual outcome

Subgroups	Trauma	Surgical aphakia	Dropped nucleus/ IOL	Subluxated/ dislocated lens-induced glaucoma	Paediatric/ Adolescents
No.	10	33	8	5	5
Mean age (years)	37	65.91	66.25	65.80	11.8
Preop BCVA	1.450 ± 0.97	0.752 ± 0.3726	1.113 ± 0.8576	2.04 ± 1.144	1.7 ± 1.237

Subgroups	Trauma	Surgical aphakia	Dropped nucleus/ IOL	Subluxated/ dislocated lens-induced glaucoma	Paediatric/ Adolescents
Postop BCVA 1 week	0.34 ± 0.255	0.409 ± 0.225	0.7 ± 0.568	0.76 ± 0.7893	0.34 ± 0.1140
Postop BCVA 1 month	0.34 ± 0.245	0.29 ± 0.207	0.57 ± 0.304	0.7 ± 0.8426	0.320 ± 0.109
Long-term follow-up BCVA > 1 year	0.3 6 ± .313	0.241 ± 0.203	0.65 ± 0.3559	0.325 ± 0.457	0.28 ± 0.13

Discussion

The aim of posterior IFIOL lens implantation is to achieve acceptable refractive and visual outcomes in patients with insufficient capsular support for intracapsular or sulcus placement of IOL while avoiding the need for aphakic spectacles or contact lenses.[5] The posterior IFIOL fixation behind the iris plane at the nodal point of the eye combines the advantages of a posterior chamber lens and a short operation time as well as an easy operation technique.[6]

In the present study, 96.43% patients achieved a BCVA better than or equal to their preoperative BCVA and 66.6% of patients achieved a final BCVA of ≥ 6/12. This is comparable to the 60% reported by De Silva *et al.*[8] and 63.5% by Gonnermann *et al.*[9] In adult study groups with no ocular comorbidity, Bhandari *et al.*[10] and Rao *et al.*[11] have reported 70% and 80% patients achieving a BCVA ≥ 6/12, respectively, with the same model of IFIOL. In the current study, on evaluating the surgical aphakia group, with no ocular comorbidity, 95.4% patients achieved BCVA ≥ 6/12. The spherical equivalent values were reduced postoperatively from + 8.25 D and -0.41 D, indicating IFIOL was well placed and good surgical technique for aphakic patients.

On subgroup analysis, the best visual outcome was attained in the post-cataract surgical aphakia group, understandably due to less ocular comorbidity, followed by the paediatric/adolescent group. In the latter group, all five of the children had had secondary IFIOL implantation post-trauma, four of which were following penetrating corneoscleral injuries. On long-term mean follow-up, they attained a statistically significantly better BCVA of 0.28 ± 0.13. In the immediate postoperative period, secondary glaucoma and endophthalmitis were identified

in one child each and successfully managed. They were all undergoing occlusion therapy to avoid amblyopia. Paediatric eyes stand to benefit from minimal manipulation of the sclera and trabecular meshwork, nil sutures, and shorter general anaesthesia span, especially in those children needing multiple surgeries with good long-term results.

In the trauma group, with five post-penetrating corneoscleral injuries and five post traumatic dislocation /subluxation of lens, a statistically significant better BCVA of 0.36 ± .313 was seen at long-term follow-up of > 1 year. Posterior IFIOL is thus a viable option in traumatic aphakia,[13] especially in penetrating corneoscleral injuries with scarred sclerae and corneas where SFIOL and ACIOL are not wise options.

Patients with subluxated/dislocated lens-induced glaucoma who underwent trabeculectomy + IFIOL implantation as a primary procedure and the nucleus/IOL drop group fared poorer in terms of visual outcome on account of their ocular comorbidities. In the former group, owing to late presentation, two of the five patients went into glaucomatous optic atrophy, while the other three had a mean BCVA of 0.2 with well controlled IOP at one-month and long-term follow-up. In the latter group, two patients with RD and one with postoperative CME improved to 0.7 and 0.2 Log MAR, respectively, on long term follow-up.

The most common complication noted here was minimal pigment deposition on the corneal endothelium in 65.7% of the patients. Pupil irregularities and anterior synaechiae were noted in the penetrating injury patients. Mild temporal ovalisation was seen in 14.2%, similar to the Bhandari *et al.* report of 10%[10] and Gonnermann *et al.* of 13.9%.[9] Pupil ovalisation can be attributed to fixation of the haptic very tightly or asymmetrically. IFIOL decentration was noted in two patients (5.7%), in agreement with other studies.[8,10] Inadequate tissue grasping during clipping may have caused the iris-claw haptics to become detached in the long term. However, a complete IFIOL dislocation into the vitreous cavity, when both haptics are detached from their attachment point coincidentally or concomitantly, has not yet been reported in the literature.

On OCT evaluation, ERM was found in 14.3% (n = 5) mostly attributable to past retinal surgery and laser. CME found in 8.57% (n = 3) similar to other studies,[9] responded well to posterior subtenon triamcinolone injections. Mean macular thickness in other patients was within normal limits.

A limitation of the current study is that endothelial specular counts were not performed preoperatively. However, earlier studies[14,15] have shown that owing to its distance away from the corneal endothelium, IFIOL is a safe procedure. No corneal decompensation was encountered in the current study. But long-term cohort studies are necessary to evaluate endothelial cell loss, especially in those patients undergoing multiple surgeries.

IFIOLs have been around for nearly four decades with mixed results. Most of the problems and complications with the earlier versions have been solved with improved design, manufacturing techniques, and surgical technique, thanks to the efforts of its inventors Dr. John Worst and Dr. Daljit Singh.[1,6,7,15,16,17,18]

Conclusion

The long-term results demonstrate that posterior IFIOL implantation is a safe and effective method for correction of aphakia in patients without capsule support. It may be considered an easier and faster option with minimal manipulation to anterior segment structures in paediatric and post-traumatic aphakic eyes.[5-7,10,13] Further long-term studies are required to evaluate the intraocular position of IFIOL in the growing eyes of children and the endothelial cell loss in different etiological types of aphakia.

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