Journal of the South East Asia Glaucoma Interest Group

Volume 10 Number 5 October and
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Asian Journal of OPHTHALMOLOGY

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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 and became the official journal of SEAGIG in 2003, 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
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Quarterly Publication

Asian Journal of OPHTHALMOLOGY is pleased to announce that, from Volume 11 2009, the publication dates will change from bimonthly to quarterly. The publication months will now be: March, June, September, and December. The extent will increase to 64-72 pages.

This development is in response to an increase in manuscript submissions, enabling us to include more high-quality manuscripts in each issue. Manuscripts may be submitted on-line via the SEAGIG website, at: www.seagig.org, or by e-mail, to: manuscripts@seagig.org.

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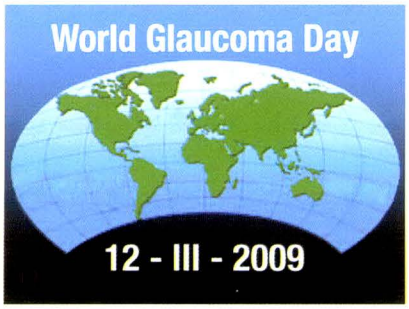
World Glaucoma Day 2009

12 March 2009, Global

The second World Glaucoma Day (WGD) will be held on 12 March 2009. World Glaucoma Day is a joint global initiative of the World Glaucoma Association and the World Glaucoma Patient Association. The intention of WGD is to increase community awareness of glaucoma and of the need to have regular eye checks, thereby permitting earlier detection and avoidance of what should be preventable visual disability.



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Conjunctival Erosion after Glaucoma Drainage Implant Surgery

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Since the introduction of the Molteno tube in 1969, glaucoma drainage implants (GDIs) have been used in the treatment of eyes with complicated glaucoma.[1] GDIs are associated with complications such as tube migration, tube or plate exposure or extrusion, ocular motility disturbance, and infection.[2] In the 1-year results of the Tube Versus Trabeculectomy Study, Gedde et al found postoperative complications in 34% of patients with tube implants.[3] Despite offering the possibility of sustained aqueous drainage for eyes at high risk for trabeculectomy failure, clearly implantation of a glaucoma drainage device is far from a benign procedure.

Erosion of the conjunctiva and exposure of the GDI are risk factors for the development of endophthalmitis. In a series of 542 eyes implanted with the Ahmed glaucoma valve (AGV), conjunctival erosion overlying the AGV was present in 6 of the 9 eyes that developed endophthalmitis.[4] This observation underscores the need to provide durable coverage for exposed GDIs to avoid this devastating complication. In this context, the choice of material used to cover the GDI tube at the time of surgery is a critical consideration that forms the basis of a successful postoperative course for the patient.

Perhaps reflecting the absence of an 'ideal' material for GDI coverage, a wide range of materials have been used for this purpose, including sclera, dura, pericardium, fascia lata, and cornea.[5-12] There is no clear evidence that any of these methods is superior to another for providing tectonic durability in the long term.[13]

In this issue of *Asian Journal of Ophthalmology*, Leuenberger et al describe their experience with the use of donor and autologous scleral patch graft in covering the AGV tube at the time of implantation.[14] In a retrospective review of 11 patients with autologous scleral patch and 14 with donor scleral patch grafts followed up for a median of 20 and 53 months, respectively, the authors found an exposure rate of 0% and 71%, respectively. The authors explain this difference as being possibly due to toxic effects of residual absolute alcohol retained in the donor sclera, in addition to increased mechanical friction between tarsal and bulbar conjunctiva due to the relative protrusion of the explant and graft in the donor sclera eyes compared with the autologous sclera eyes. This report is also notable in that 2 eyes developed endophthalmitis after conjunctival erosion and GDI tube exposure. It would be interesting to review the same cohort of patients after extended follow-up of the patients in the autologous graft group.

Clinicians may find scant guidance in the literature with regards to the best method to resolve the challenging problem of tube exposure; repeated attempts at repair may be necessary in the face of a hypotonous eye at risk for infection. Surgeons may find it intuitive to perform direct closure of dehisced conjunctiva. However, scarring at the site of GDI implantation and poor conjunctival status due to chronic use of medications greatly reduce the chances of success. Conjunctival, scleral, and amniotic membrane grafts have been reportedly used in the repair of exposed GDIs. Our group has used cornea patch grafts for the repair of GDI tube exposure.[15] We found cornea to be a durable material for the repair of conjunctival erosions, even in patients with multiple previous failed attempts at repair.

The ideal material for primary cover of GDIs would have to be resistant to melting over the long term and have the ability to integrate well with the tissues surrounding the GDI tube. The development of such a material will offer better outcomes for the management of patients with complex glaucoma.

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Ahmed Glaucoma Valve Tube Erosion: a Retrospective Comparative Review of Autologous Scleral Patch Versus Donor Scleral Patch Grafts

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Aim: *To determine the amount of tube erosion among patients implanted with the Ahmed glaucoma valve using autologous scleral patch or donor scleral patch graft.*
Methods: *This was a retrospective comparative review of an interventional consecutive case series of Ahmed glaucoma valve implantation using autologous scleral patch or donor scleral patch graft to cover the Ahmed glaucoma valve tube. The primary outcome measure was tube erosion, and the secondary outcome measure was complications associated with tube erosion. Tube erosion was defined as tube exposure visible by slit-lamp examination.*
Results: *Twenty five eyes of 25 consecutive patients underwent Ahmed glaucoma valve implantation. Fourteen eyes received donor scleral patch grafts and 11 eyes received autologous scleral patches. No erosions were noted in the autologous scleral patch group. However, 71% of eyes in the donor scleral patch graft group had transconjunctival erosions. Two of 25 eyes (8%) developed endophthalmitis; transconjunctival erosion was present in both of these eyes.*
Conclusions: *The use of autologous scleral patch with Ahmed glaucoma valve implantation appears to be an effective technique for preventing transconjunctival tube erosion. Exposure of the tube is a major risk factor for the development of endophthalmitis.*

Key words: *Endophthalmitis, Glaucoma drainage implants, Tissue donors, Transplantation, autologous, Transplants*

Asian J Ophthalmol. 2008;10:347-53

Introduction

Glaucoma drainage devices (GDDs) such as the Ahmed glaucoma valve (AGV; New World Medical, Rancho Cucamonga, USA) play an important role in the treatment of glaucomas for which trabeculectomy is likely to fail. These glaucomas include neovascular glaucoma, uveitic glaucoma, aphakic and pseudophakic glaucoma, and extremely scarified conjunctiva, as well as previous failed filtering procedures.

The AGV consists of a valved plate body connected to a tube. The valved plate body has 2 variants — medical grade polypropylene (model S2) or medical grade silicone (model FP7), both with a surface area of 184 mm^2. The tube connected to the plate is made of medical grade silicone and has an uncut length of 25 mm, with an outer diameter of 0.635 mm and an inner diameter of 0.305 mm. The valve mechanism consists of thin silicone elastomer membranes, which are 8 mm long and 7 mm wide and create a Venturi-shaped chamber. The membranes are pretensioned to open and close in response to changes in intraocular pressure (IOP). The Venturi-shaped chamber uses Bernoulli's principle to help drain aqueous humour from the eye. This principle states that the velocity of fluid increases as it moves from a larger inlet to a smaller outlet port. As the inlet cross-section is wider than the outlet, a pressure differential is created across the chamber. This pressure differential enables the valve to remain open even with a small pressure differential between the anterior chamber and subconjunctival space surrounding the AGV.[1]

The silicone tube of the AGV connects the anterior chamber or posterior chamber to the equatorial region of the globe where the AGV plate is implanted. Aqueous is shunted in a unidirectional manner through the valve mechanism and pools in the space between the valve plate and the posterior bleb encapsulation. The aqueous humour then penetrates the posterior bleb encapsulation

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and is eventually absorbed by the lymphatics and capillaries of the orbital tissues. Minckler et al demonstrated movement of latex microspheres as large as 0.2 μm passing freely through the capsular wall.[2]

At implantation of the AGV, the subconjunctival and sub-Tenon's portion of the tube is covered with a patch graft of donor sclera, human allograft tissue of gamma sterilised sclera and pericardium, donor dura mater, fascia lata, or tectonic corneal patch graft. Alternatively, a limbal-based scleral lamellar patch graft similar to the scleral flap used for trabeculectomy procedures may be used.[3]

These authors hypothesise that the use of an autologous scleral patch graft is an effective, safe, easily available, and inexpensive alternative to donor scleral patch grafts, that also offers the advantage of minimising the risk of infectious disease transmission. To date, no Asian study has been undertaken to compare the efficacy of autologous scleral patch versus donor scleral patch graft for preventing transconjunctival AGV tube erosion and describe the complications surrounding its use. This study aims to determine the amount of tube erosion among patients implanted with the AGV using autologous scleral patch or donor scleral patch graft, and reports the surgical technique and the management of related complications.

Methods

Patients

The medical records of 25 eyes of 25 consecutive patients with glaucoma, who underwent AGV implantation using either autologous scleral patch or donor scleral patch graft at an urban eye centre in Manila, The Philippines, between August 2001 and April 2006 were retrospectively reviewed. Eleven patients (44%) underwent AGV implantation using autologous scleral patch and 14 (56%) had AGV implantation with donor scleral patch graft. Either donor or autologous scleral patches were used according to the surgeon's preference. No data were available from the eye bank where the donor scleral patches were obtained, and the site of harvest (posterior or limbal) was not mentioned. The donor scleral patches were hydrated but not thinned before use.

The inclusion criteria for the medical records were demographic data, preoperative indications for surgery, operative techniques of AGV implantation, manner of preparing the donor sclera, postoperative notes and photographs by the attending surgeon describing the appearance of the AGV tube and conjunctiva, including tube erosions and their associated complications, and operative intervention and techniques for managing complications. Sixteen patients were excluded from the study due to insufficient data or inability to meet the inclusion criteria. Data entries were collected using a standardised form and were reviewed by 2 investigators. Visual acuity, IOP control, and lens status were not included in the data gathering and analysis.

All study eyes were evaluated by slit-lamp biomicroscopy at each follow-up visit. Photographs were taken as needed. To be eligible for inclusion in the study, all patients were required to have completed a minimum of 4 months follow-up from the date of the AGV implantation.

Transconjunctival tube erosion was defined as any part of the AGV tube exposed through the conjunctiva, and visible by biomicroscopic examination. Seidel's test was not included in the criteria for evaluating tube erosion but was included as a risk factor for developing endophthalmitis.

Surgical Procedure

Two experienced surgeons performed the AGV implantation. All patients received intraoperative sedation. One surgeon used topical anaesthesia with supplemental subconjunctival lidocaine, while the other surgeon used retrobulbar block. One surgeon used donor scleral patch grafts for all procedures, while the other surgeon used donor scleral patch grafts then autologous scleral patch consecutively. General anaesthesia was used for a child with congenital aniridia. Both surgeons used the same operative technique of AGV implantation and the procedure was standardised to avoid bias. Of the 25 eyes, 21 received the AGV model S2 (polypropylene plate body) while 2 eyes in the autologous scleral patch group and 2 eyes in the donor scleral patch graft group received the AGV model FP7 (silicone plate body).

After administration of anaesthesia, a limbal corneal 6-0 or 7-0 silk traction suture was applied. A 3–clock hour superotemporal limbal conjunctival incision was created and relaxed on each side. Spring tenotomy scissors were used to carry the dissection posteriorly towards the equator to create a pocket between the superior and lateral recti muscles. Bleeding was controlled with bipolar cautery. The AGV plates were separated by irrigating the AGV tube with balanced salt solution (BSS) using a 27 G cannula. The AGV was held by the eyelets with forceps and tucked into the posterior pocket with the anterior border of the AGV plate approximately 8 mm away from the limbus. The AGV plate was anchored to the underlying sclera through the eyelets with 9-0 nylon sutures on a spatulated needle. A paracentesis was created with a 15° blade and hyaluronic acid viscoelastic solution was injected into the anterior chamber. The tube was cut to length, bevel up, and a limbal sclerostomy was created using a 23 G needle. Additional viscoelastic was injected through the limbal sclerostomy followed by insertion of the tube into the anterior chamber. The body of the tube was then anchored to the sclera with interrupted 9-0 nylon sutures. Prior to use, the donor scleral patch graft was

soaked in BSS for 30 minutes. The donor sclera was then cut to size and used to cover the body of the tube; 9-0 nylon sutures were used to anchor the donor sclera to the host sclera (Figure 1).

For the autologous scleral patch group, a 7- x 7-mm limbal-based lamellar scleral flap was constructed with a crescent knife, the tube was inserted through a limbal sclerostomy under the flap, and the flap was anchored with 9-0 nylon sutures (Figure 2). The conjunctiva was then repositioned and reattached to the limbus with interrupted 10-0 nylon sutures.

Statistical Analysis

The following variables were evaluated: age and sex, indications for AGV implantation, number and type of previous conjunctival surgeries, type of glaucoma, time from implantation of the AGV to recorded transconjunctival erosion, complications associated with erosions, and interventions after erosions were noted.

Descriptive statistics consisted of measures of central tendency (mean and SD) for continuous numerical data and percentage-frequency distribution for categorical variables. Comparison of categorical data was done using the Chi-squared test and Mann-Whitney *U* test for continuous numerical data. Comparison of proportion of subjects with tube erosion (main outcome measure) in both groups was facilitated using the Z test of 2 proportions.

Statistical analysis was performed using STATISTICA (Statsoft version 1991 licensed software). A p value of <0.05 was considered statistically significant.

Figure 1. Donor scleral patch graft over the Ahmed glaucoma valve tube.

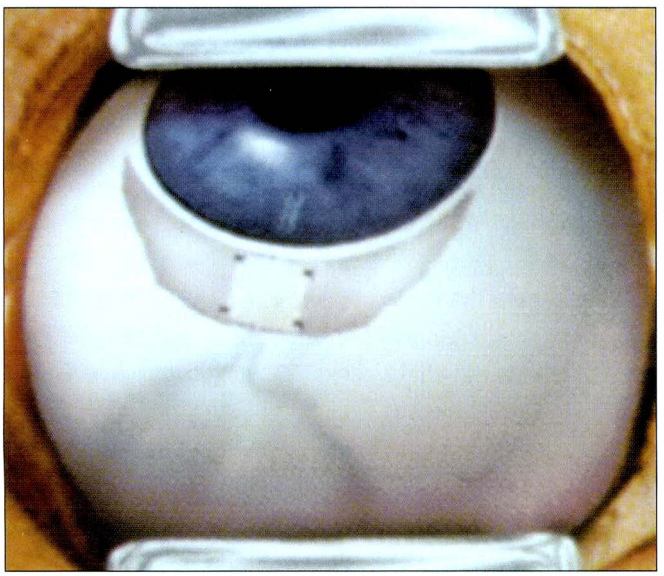
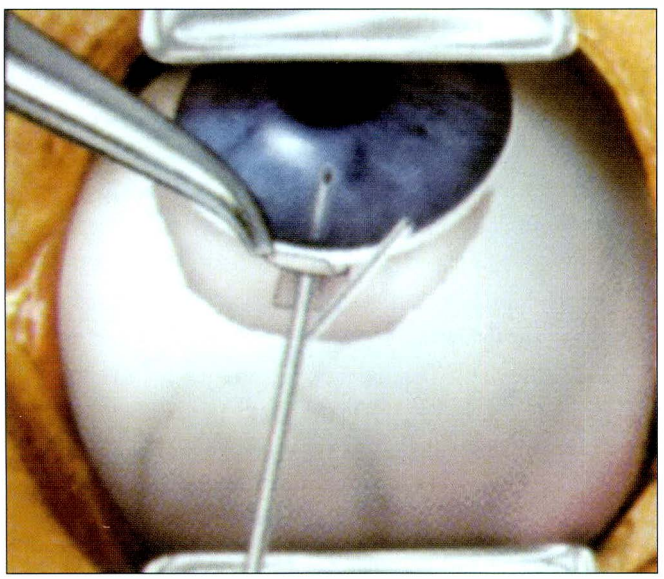


Figure 2. Autologous scleral patch.



Results

There were 41 GDD surgeries performed between August 2001 and April 2006 at the Asian Eye Institute, Manila, The Philippines, 16 of which were excluded from the study because they did not meet the entry criteria. Twenty five eyes with glaucoma were identified for inclusion in the study. Eleven eyes (44%) underwent Ahmed valve tube implantation using autologous scleral patch and 14 (56%) had donor scleral patch grafts (Table 1). Four patients in the donor scleral patch graft group were eventually lost to follow-up but had completed the minimum follow-up period. No patients were lost to follow-up in the autologous scleral patch group.

The mean age was 51 years (SD, 3 years; range, 9 to 84 years). The youngest patient was a 9-year-old girl with congenital aniridia, who underwent AGV implantation with autologous scleral patch, and the oldest patient was an 84-year-old man who underwent AGV implantation with donor scleral patch graft. There were 18 men and

Table 1. Demographic and clinical characteristics of patients with glaucoma undergoing Ahmed glaucoma valve implantation.

Characteristic	Donor scleral patch graft (n = 14) Number (%)	Autologous scleral patch (n = 11) Number (%)	p Value*
Age (years)			0.33
0-10	0 (0)	1 (9)	
11-20	1 (7)	1 (9)	
21-30	2 (14)	1 (9)	
31-40	2 (14)	0 (0)	
41-50	1 (7)	1 (9)	
51-60	3 (21)	3 (27)	
61-70	3 (21)	2 (18)	
71-80	1 (7)	2 (18)	
81-90	1 (7)	0 (0)	
Sex			0.06
Male	12 (86)	6 (54)	
Female	2 (14)	5 (46)	
Affected eye			0.22
Right	9 (64)	8 (73)	
Left	5 (36)	3 (27)	

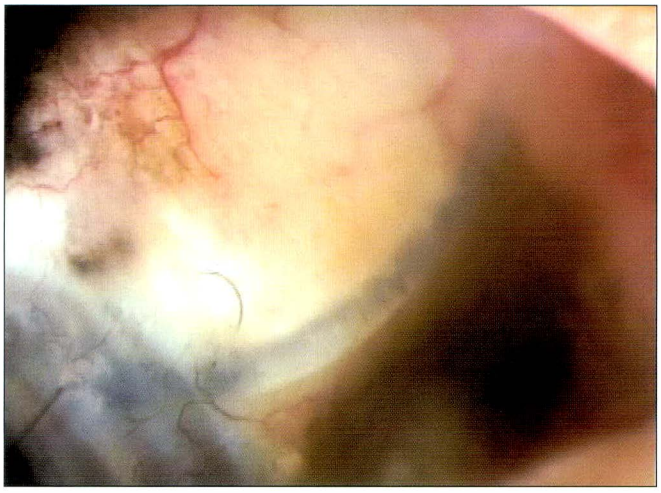
* Chi-squared test.

Table 2. Tube erosion among patients with glaucoma undergoing Ahmed glaucoma valve implantation.

Tube erosion	Donor scleral patch graft (n = 14) Number (%)	Autologous scleral patch (n = 11) Number (%)	p Value*
Present	10 (71)	0 (0)	0.29
Absent	4 (29)	11 (100)	

* Z test of 2 proportions.

Figure 3. Appearance of the tube under an intact conjunctiva 1 year after autologous lamellar scleral patch.



7 women. The right eye was more frequently involved than the left eye (68% versus 32%). There were no significant differences in age, sex, or laterality (p = 0.33, p = 0.06, and p = 0.22, respectively).

Table 2 shows the number of patients with and without tube erosion. There were no tube erosions observed among those receiving autologous scleral patch (Figure 3) and 10 tube erosions (71%) among those receiving donor scleral patch grafts. However, this difference was not statistically significant (p = 0.29).

Half of the tube erosions in the donor scleral patch graft group occurred during the first 3 postoperative months; the earliest occurred 1 month postoperatively and the latest occurred between 37 and 39 months (average, 3 years postoperatively) [Table 3].

The number of previous conjunctival surgeries did not differ statistically between the 2 groups. Previous conjunctival procedures accounted for the majority of the indications for the AGV procedure, with a greater number in the donor scleral patch graft group (10 of 14 eyes; 71.4%) than in the autologous scleral patch group (6 of 11 eyes; 54.5%). Neovascular glaucoma was the second most frequent indication for the procedure in both the donor scleral patch graft group (3 of 14 eyes; 21.4%) and the autologous scleral patch group (4 of 11 eyes; 36.4%) [Table 4].

Table 3. Cumulative frequency of tube erosion among patients with glaucoma receiving donor scleral patch graft.

Erosion time (months)	Erosion rate (n = 10) Number (%)
0-3	5 (50)
7-9	1 (10)
16-18	1 (10)
19-21	1 (10)
25-27	1 (10)
37-39	1 (10)

Two of 25 eyes (8%) developed endophthalmitis (Table 5 and Figures 4 and 5). Conjunctival erosion was present in both eyes, and these eyes required explantation of the AGV. In one of the eyes, tube culture studies yielded *Staphylococcus* spp, but culture studies were not available for the other patient. Both eyes underwent diode cyclophotoablative laser treatment for subsequent IOP control.

Four patients with transconjunctival tube erosions were noted to have sterile hypopyon (Figure 6), 2 of whom underwent amputations of the tube leaving a short tube stump and the AGV plate body untouched. The limbal sclerostomy and conjunctival defects were closed and trabeculectomy with mitomycin C was performed in adjacent areas where the conjunctiva was deemed mobile. For the third patient, the AGV was explanted and replaced with a new AGV using a donor scleral patch graft. No new erosions were noted during the follow-up period. Resolution of the hypopyon was noted within the first week of the intervention.

Three patients with tube erosions did not show any intraocular sequelae for more than 36 months from the time the erosion was noted. These patients have been Seidel test negative and their eye health is maintained by rotating third- and fourth-generation topical antibiotics given once daily since the erosion was noted (Figure 7).

Patients receiving donor scleral patch graft were followed up for 36 to 70 months (mean, 53 months) and those receiving autologous scleral patch were followed up for 4 to 36 months (mean, 20 months).

Discussion

Although studies have shown the efficacy of the AGV for the treatment of complicated glaucomas, several complications have been reported. These include hypotony,[4] tube blockage or valve failure,[5] loss of visual acuity,[6] strabismus and diplopia,[7] epithelial downgrowth,[5] calcification of the implant,[8] transconjunctival and/or tube erosion,[9] transconjunctival plate erosion, plate extrusion, and associated endophthalmitis.[9]

Retrospective studies have shown that endophthalmitis is a rare complication after GDD implantation, including the AGV.[9] In a retrospective review of 542 eyes implanted with the AGV, endophthalmitis developed in 9 eyes (1.7%).[9] It has been suggested that a Seidel-positive transconjunctival AGV tube erosion in a young patient represents a major risk factor for the development of

Table 4. Diagnosis of patients with glaucoma undergoing Ahmed glaucoma valve implantation.

Diagnosis	Donor scleral patch graft (n = 14) Number (%)	Autologous scleral patch (n = 11) Number (%)
Post–extra capsular cataract extraction open angle glaucoma	2 (14.2)	1 (9.0)
Post–retinal detachment surgery open angle glaucoma	2 (14.2)	2 (18.1)
Post–filter chronic angle closure glaucoma	1 (7.1)	1 (9.0)
Neovascular glaucoma	3 (21.4)	4 (36.3)
Uveitic glaucoma	1 (7.1)	1 (9.0)

Table 5. Complications and interventions for patients with Ahmed glaucoma valve (AGV) tube erosions.*

Complication	Intervention	Number of patients (%) [n = 25]
Endophthalmitis	Valve explanted, vitrectomy, infective agent unknown	1 (4)
	Valve explanted, *Staphylococcus* spp on tube culture, diode transcleral cyclophotoablative laser	1 (4)
Sterile hypopyon (anterior uveitis)	Tube amputated, valve plate retained, trabeculectomy with mitomycin C	2 (8)
	Tube amputated, valve plate retained, new AGV implanted inferiorly	1 (4)
Erosion with no intraocular sequelae	AGV explanted, new AGV implanted, no further erosion	1 (4)
Erosion with no intraocular complications	36 months since erosion†	1 (4)
	43 months since erosion†	1 (4)
	48 months since erosion†	2 (8)

* Donor scleral patch graft group only.
† Seidel test negative, maintained with topical third- and fourth-generation fluoroquinolones once daily.

Figure 4. Tube erosion with exudates (*Staphylococcus* spp) seen 3 months after Ahmed glaucoma valve implantation with donor scleral patch graft. The patient developed endophthalmitis and underwent Ahmed glaucoma valve explantation and vitrectomy. Diode transcleral cycloablation was done to control the intraocular pressure.

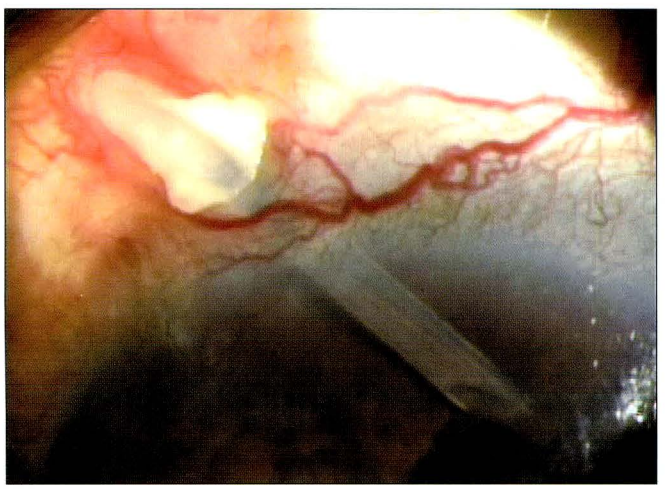
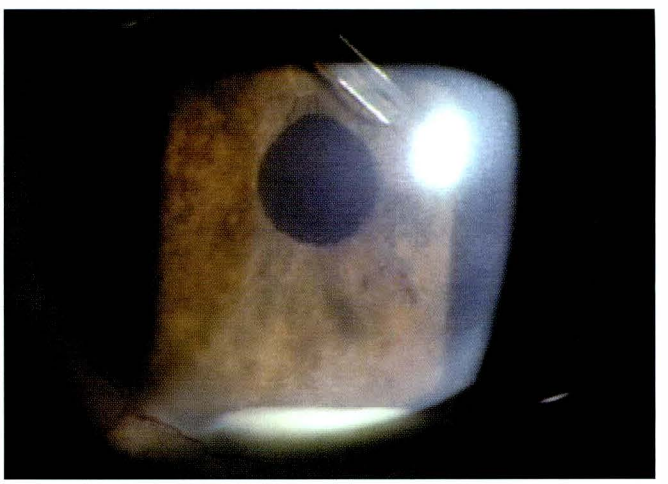


Figure 5. Hypopyon associated with tube erosion.



endophthalmitis. In all of the surgeries, the tube was covered with either sclera, dura, or pericardial patch graft. Autologous scleral patch was not used for any of the procedures.

In a retrospective study by Aslanides et al involving 17 eyes and using a variety of GDDs with autologous scleral patches, no eyes showed clinical evidence of tube erosion or graft-related intraocular complications after a mean follow-up of 14.8 months (range, 6 to 62 months).[3] Smith et al reported that no tube covering material was superior to any other.[10]

It is interesting to note that all erosions noted in this study occurred in the donor patch graft group. It is possible that many factors lead to transconjunctival erosion of the AGV tube. Minute amounts of absolute alcohol could be retained in the donor sclera, causing toxic effects to the ocular tissues and resulting in tube erosions.[11] Using gas chromatography studies, Enzenauer et al have shown that scleras preserved in 95% alcohol leach only 98% of the alcohol after soaking in BSS for ≥20 minutes, while 2% remains in the sclera.[12] It is therefore uncertain whether soaking the donor sclera in BSS for 30 minutes was sufficient to leach the absolute alcohol used as a preservative by the local eye bank.

Mechanical friction from constant rubbing of the eyelids against the conjunctiva and patch graft may contribute to erosion, but the exact mechanism is unknown.[13] These authors hypothesise that burying the tube under an autologous lamellar scleral patch graft could reduce the overall height of the tube and the graft. The

Figure 6. Sterile hypopyon and anterior uveitis associated with Ahmed glaucoma valve transconjunctival tube erosion in a patient with donor scleral patch graft. The tube was explanted and amputated leaving the valve plate in the eye. Trabeculectomy with mitomycin C was done to control the intraocular pressure.

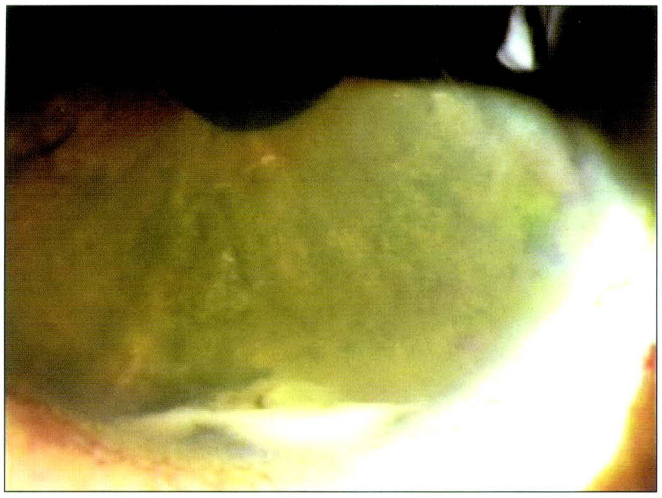
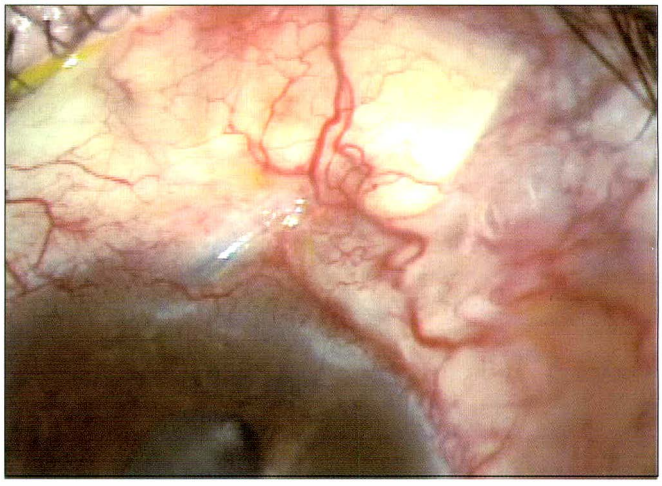


Figure 7. Seidel test–negative transconjunctival tube erosion in a patient with an Ahmed glaucoma valve. The scleral donor patch graft shows partial melt. The patient was asymptomatic with no introcular sequalae.



overlying conjunctiva would be subject to reduced tension and mechanical friction. This could be important, as the majority of patients in this study had pre-existing scarred conjunctiva from previous surgeries.

A thick donor sclera may result in more mechanical friction against the blinking eyelids, leading to erosion. The area of the donor sclera immediately posterior to the insertions of the recti muscles may be more suitable for a patch graft as this sclera is anatomically thinner (0.3 mm versus 1.0 mm for the region surrounding the optic nerve).[14]

The high occurrence of transconjunctival erosions observed among patients receiving the donor scleral patch graft prompted the authors to change technique to use autologous scleral patch, as this was not associated with conjunctival erosion. This explains the shorter follow-up period for the latter group of patients. However, the limited sample size of this study did not permit meaningful statistical comparisons between the 2 groups. There were also no data available about the donor sclera that could have an effect on tube erosion.

Endophthalmitis developed in 2 of the 25 eyes (8%). Early treatment of patients with erosion and hypopyon (3 of 10 eyes) may have helped to avoid this complication. Four of 10 eyes with erosion were Seidel test negative with no intraocular signs of inflammation. These patients had regular follow-up and antibiotic prophylaxis, and were aware of the early signs of inflammation. Some authors have suggested that exposed GDD tubes may be observed in the absence of a leak (Seidel test negative) or ocular irritation.[15] It is not clear whether prophylactic topical antibiotic maintenance is of any clinical benefit.

This retrospective comparative review of 25 eyes undergoing AGV implantation and either donor scleral patch graft or autologous scleral patch provides insight as to which technique is most effective for preventing transconjunctival tube erosions. The use of autologous scleral patch did not result in any transconjunctival tube erosions. To validate these conclusions, it is recommended that this cohort be followed up for a longer period of time. Furthermore, collateral studies to investigate the technique for preparing the donor sclera may help to explain the high occurrence of transconjunctival tube erosions in this group. A comparison of the different solutions used for rinsing off the preservative ethanol could be undertaken and investigation of the role of mechanical friction on the conjunctiva overlying the patch graft and ultrabiomicroscopic studies measuring graft heights may provide valuable information. To control the multiple variables identified, a prospective comparison between the 2 patch graft groups is recommended. Comparing erosion rates between locally procured donor sclera versus donor sclera obtained from other countries may also be of value.

In summary, the use of autologous scleral patch for AGV implantation resulted in a significantly better outcome than donor scleral patch grafts. It is important to consider all the factors that may be related to tube exposure after implantation, starting from the procurement of the sclera, preservation techniques, and rinsing agents used by institutions performing GDD implantation using either autologous scleral patch or donor scleral patch graft.

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Time Interval for the Development of Posterior Capsular Opacification in Different Intraocular Lenses in Asian Eyes

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Aim: *To evaluate the time interval to the development of visually significant posterior capsular opacification associated with different intraocular lenses and to assess the impact on visual acuity.*
Methods: *150 eyes of 127 patients with cataract who had undergone Nd:YAG laser capsulotomies from January to October 2007 were evaluated. All eyes had undergone standardised phacoemulsification and intraocular lens implantation in the capsular bag. Intraocular lenses implanted included acrylic with a sharp edge, silicone with a sharp edge, and silicone with a round edge. Postoperatively, posterior capsular opacification was assessed by slit-lamp examination using retroillumination. The time interval for development of visually significant posterior capsular opacification and need for Nd:YAG laser capsulotomy was noted.*
Results: *There were 70 women and 57 men. For acrylic intraocular lenses with sharp edge, the mean time to development of visually significant posterior capsular opacification was 26.91 months (SD, 9.18 months) for the Akreos Adapt, 37.69 months (SD, 19.90 months) for the MA60BM, 53.17 months (SD, 19.88 months) for the Ar40e, and 38.43 months (SD, 8.89 months) for the 1CU. For silicone intraocular lenses with a sharp edge, the mean time to development of visually significant posterior capsular opacification was 17.93 months (SD, 6.35 months) for the ZM900, 37.93 months (SD, 20.69 months) for the SA40N, and 25.14 months (SD, 3.34 months) for the Z9000 ($p = 0.001$). For the silicone intraocular lens with round edge (SI40NB), the mean time to development of visually significant posterior capsular opacification was 16.80 months (SD, 13.07 months).*
Conclusions: *There was a wide variation in time to development of visually significant posterior capsular opacification among the different intraocular lenses implanted after cataract surgery. This has important implications for the future development of intraocular lenses and for the choice of intraocular lens made by surgeons treating patients with cataract.*

Key words: *Cataract extraction, Lens, crystalline, Lens implantation, intraocular*

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Introduction

Posterior capsular opacification (PCO) is the most common post-operative complication after routine cataract surgery,[1,2] with rates of up to 50% reported 2 to 3 years after cataract surgery.[1] PCO results from retained lens epithelial cells in the anterior capsule,[1,3] which proliferate and differentiate into myofibroblasts, resulting in thickening of the capsular bag and occlusion of the visual axis.[1,3]

PCO formation is multifactorial. Patient factors, surgical techniques, and intraocular lens (IOL) material and design have been implicated in the pathogenesis. Patient factors that may contribute to formation of PCO include young age,[4,5] uveitis,[6,7] and diabetes mellitus.[8,9] Surgical factors include loss of rhexis and IOL contact.[10] Several authors have found that making a small central capsulorrhexis and encasing the IOL optic with the rhexis edges protects against PCO.[11-13] Complete removal of cortical and lens material also reduces the incidence of PCO.[14-16]

IOL factors that influence PCO development include the design of the optic edge,[17-23] optic material,[11,18,24-26] haptic design,[14] and optic size.[3] Cheng et al found that sharp-edged IOLs are associated with lower rates of PCO than round-edged IOLs.[18] Similar results have been noted in other studies.[17-23,27] Cheng et al[18] and Hayashi et al[28] found that acrylic and silicone IOLs are associated with lower rates of PCO than polymethyl methacrylate (PMMA) IOLs, and several studies have found that acrylic IOLs are associated with lower rates of PCO than silicone IOLs.[11,18,24-26]

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Sacu et al suggested that some capsular bend configurations have a greater barrier effect than others.[27] Sun suggested that IOLs should have stronger haptics and greater haptic angulation to be able to stretch the posterior capsule for prevention of PCO.[14] Meacock et al found that there was less PCO among patients receiving larger optic IOLs, suggesting that the larger lens retards PCO more effectively because of the greater angulation of the haptics.[3]

Multiple factors have been found to influence the development of PCO. However, the time to development of visually significant PCO has been poorly characterised. This study aims to evaluate time to development of visually significant PCO associated with IOLs of different material (silicone versus acrylic) and edge design (square edge versus round edge), and to assess the impact on visual acuity in Asian eyes.

Patients

150 eyes of 127 consecutive patients with cataract who had undergone Nd:YAG laser capsulotomies at the National University Hospital, Singapore, from January to October 2007 were enrolled in this retrospective study. The inclusion criteria were visually significant PCO requiring Nd:YAG laser capsulotomies. All patients had age-related cataract and had undergone standardised phacoemulsification through a clear corneal incision, with implantation of a foldable posterior chamber IOL in the capsular bag.

Patients with diabetes, ocular pathology such as uveitis, glaucoma, or retinal conditions, history of other intraocular surgery or laser treatment, or intraoperative complications such as posterior capsular rupture were excluded from the study.

Study Design

Patients were divided into 3 groups, depending on the IOL implanted at the time of surgery: an acrylic IOL with a sharp edge, silicone IOL with a sharp edge, or silicone IOL with a round edge. The decision as to which IOL to implant was made by the surgeon at the time of surgery.

Acrylic IOLs with a sharp edge included in the study were the Akreos Adapt Advanced Optics (Bausch & Lomb, Rochester, USA), AcrySof® MA60BM (Alcon Laboratories, Inc, Fort Worth, USA), Sensar OptiEdge AR40e lens (Advanced Medical Optics [AMO], Santa Ana, USA), and 1CU (HumanOptics, Broadstone, UK). Silicone IOLs with a sharp edge included the Array SA40N IOL (AMO), Tecnis ZM900 (AMO), and Tecnis Z9000 IOL (AMO). The silicone IOL with a round edge was the PhacoFlex® II SI40NB (AMO).

Akreos Adapt is a 1-piece hydrophilic acrylic IOL with a 360° double-squared edge. The MA60BM has a biconvex acrylate optic and a rectangular optic edge. The AR40e acrylic IOL is designed with a modified sharp posterior optic edge. The 1CU is a single-piece accommodating monofocal acrylic IOL with a square edge.

SA40N is a second-generation foldable silicone zonal progressive multifocal IOL with a sharp optic edge. ZM900 is a multifocal 3-piece silicone IOL with a biconvex optic and sharp optic edge. The Z9000 is a 3-piece silicone posterior chamber IOL with a biconvex optic and a modified prolate anterior surface with a sharp optic edge. SI40NB has a biconvex silicone optic, a round optic edge, and a haptic similar to the MA60BM.

Follow-up was done 1 month, 6 months, 1 year, and 3 years postoperatively. Assessment at each follow-up visit included refraction and best-corrected distance visual acuity (BCDVA) using logMAR charts, slit-lamp biomicroscopy, tonometry, and fundoscopy.

Visually significant PCO was defined as opacification of the posterior capsule in the visual axis, observed by retroillumination with slit-lamp biomicroscopy, with a reduction in BCDVA of logMAR ≥0.3 caused solely by PCO. The primary endpoints were time to development of visually significant PCO necessitating Nd:YAG laser capsulotomy, and the decrease in visual acuity.

Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences version 15.0 for Windows. Continuous variables were described as mean and standard deviation. The results for the square-edged and round-edged silicone IOL groups, and the sharp-edged acrylic and silicone IOL groups were compared, and mean values were calculated for each group. Within each group, the mean value was compared for each IOL. The linear regression test was used for statistical analysis of the time to development of visually significant PCO. A p value of <0.05 was considered significant.

Results

150 eyes of 127 patients were included in the study. There were 70 women and 57 men (Table 1). The mean age was 66.63 years (SD, 11.48 years) [Figure 1]. Patients were divided into 3 groups according to the IOL implanted: 66 eyes had an acrylic IOL with a sharp edge, 37 eyes had a silicone IOL with a sharp edge, and 47 eyes had a silicone IOL with a round edge (Table 2). There were no significant differences in characteristics between the groups.

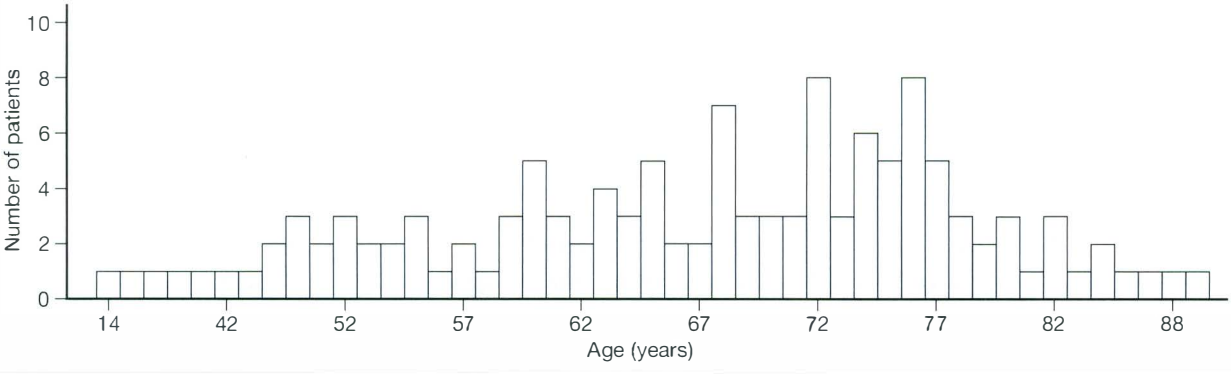
Postoperative data for all 150 eyes (100%) were available at the 1-month, 6-month, and 1- and 3-year follow-ups. The mean BCDVA at 1 month was 0.12 D (SD, 0.14 D) for the eyes with an acrylic IOL with a sharp edge, 0.06 D (SD, 0.11 D) for the eyes with a silicone IOL with a sharp edge, and 0.14 D (SD, 0.17 D) for eyes with a silicone IOL with a round edge. The mean BCDVA at 1 month for the individual IOLs are shown in Table 2.

Table 1. Characteristics of eyes of patients with posterior capsular opacification.

Intraocular lens	Number of patients (n = 127)*		Age (years) Mean (range)	Number of eyes implanted (n = 150)	
	Male	Female		Right	Left
Acrylic with sharp edge	22	36	66.3 (14-88)	36	30
Silicone with sharp edge	15	14	64.9 (35-79)	23	14
Silicone with round edge	20	20	67.5 (42-92)	23	24
Total	57*	70	65.8 (14-92)	82	68

* Twenty three patients underwent cataract surgery in both eyes.

Figure 1. Age distribution of patients with posterior capsular opacification.



The mean decrease in BCDVA in eyes that developed PCO is shown in Table 3. The decrease in visual acuity with development of PCO was not significant for the different IOL materials (acrylic versus silicone), but was significant for lens edge type, with a greater mean decrease in BCDVA for the silicone IOL with a round edge than for the silicone IOL with a sharp edge IOL ($p = 0.02$) [Table 3]. There was no significant difference in mean decrease in BCDVA between the different IOLs in the acrylic IOL with a sharp edge group ($p = 0.13$) or the silicone IOL with a round edge group ($p = 0.24$).

The mean time to development of visually significant PCO was 40.18 months (SD, 19.00 months) in the acrylic IOL with a sharp edge group and 27.41 months (SD, 16.39 months) in the silicone IOL with a sharp edge ($p = 0.001$) [Table 4]. The mean time to development of PCO in the group with the silicone IOL with a round edge was 16.80 months (SD, 13.07 months) [$p = 0.001$ compared with the other IOLs studied].

Table 2. Types of intraocular lenses implanted.

Intraocular lens	Eye (n = 150) Number (%)	BCDVA at 1 month (D) Mean (SD)
Acrylic with sharp edge (n = 66)		
Akreos Adapt	15 (10.0)	0.03 (0.07)
MA60BM	15 (10.0)	0.17 (0.16)
AR40e	20 (13.3)	0.14 (0.19)
1CU	16 (10.7)	0.09 (0.12)
Silicone with sharp edge (n = 37)		
SA40N	15 (10.0)	0.01 (0.04)
Tecnis ZM900	15 (10.0)	0.07 (0.10)
Tecnis Z9000	7 (4.6)	0.13 (0.20)
Silicone with round edge (n = 47)		
SI40NB	47 (31.3)	0.14 (0.18)

Abbreviation: BCDVA = best-corrected distance visual acuity.

Comparison of the mean time to development of visually significant PCO within the acrylic IOL with a sharp edge group showed a significant difference among the individual IOLs ($p = 0.001$); the mean time was 26.91 months (SD, 9.18 months) for the Akreos Adapt, 37.69 months (SD, 19.90 months) for the MA60BM, 53.17 months (SD, 19.88 months) for the Ar40e, and 38.43 months (SD, 8.89 months) for 1CU (Table 5).

The mean time to development of visually significant PCO among the different silicone with sharp-edge IOLs was 17.93 months (SD, 6.35 months) for the ZM900, 37.93 months (SD, 20.69 months) for the SA40N, and 25.14 months (SD, 3.34 months) for the Z9000 ($p = 0.02$) [Table 5].

At the time of development of visually significant PCO, the mean BCDVA was 0.35 D (SD, 0.22 D), 0.15 D (SD, 0.17 D), and 0.44 D (SD, 0.26 D) months for the acrylic IOL with a sharp edge, silicone IOL with a sharp edge, and silicone IOL with a round edge, respectively.

After Nd:YAG laser capsulotomy, the mean BCDVA was 0.18 D (SD, 0.18 D) for the acrylic IOL with a sharp edge, 0.09 D (SD, 0.09 D) for the silicone IOL with a sharp edge, and 0.22 D (SD, 0.19 D) for the silicone IOL with a round optic edge. The increase in BCDVA post–Nd:YAG laser capsulotomy was not significant between the acrylic (0.28 D [SD, 0.23 D]) versus the silicone (0.19 [SD, 0.20 D])

Table 3. Changes in visual acuity after development of posterior capsular opacification and post–Nd:YAG laser capsulotomy for different intraocular lenses.

Intraocular lens	Decrease in BCDVA with posterior capsular opacification (D) Mean (SD)	p Value	Improvement in BCDVA post-Nd:YAG laser capsulotomy Mean (SD)	p Value
Acrylic with a sharp edge	0.24 (0.21)		0.28 (0.23)	0.36
Silicone with a sharp edge	0.09 (0.16)	0.02	0.19 (0.20)	0.03
Silicone with a round edge	0.29 (0.27)		0.38 (0.30)	

Abbreviation: BCDVA = best-corrected distance visual acuity.

Table 4. Time to development of posterior capsular opacification for different intraocular lenses.

Intraocular lens	Time (months) Mean (SD)	p Value
Acrylic with a sharp edge	40.18 (19.00)	0.001
Silicone with a sharp edge	27.41 (16.39)	
Silicone with a round edge	16.80 (13.07)	0.001

Table 5. Time to development of posterior capsular opacification according to type of intraocular lenses implanted.

Intraocular lens	Time (months) Mean (SD)	Number of eyes
Acylic with a sharp edge (n = 66)		
Akreos Adapt	26.91 (9.18)	15
MA60BM	37.69 (19.90)	15
AR40e	53.17 (19.88)	20
1CU	38.43 (8.89)	16
Silicone with a sharp edge (n = 37)		
ZM900	17.93 (6.35)	15
SA40N	37.93 (20.69)	15
Z9000	25.14 (3.34)	7

IOL with a sharp edge (p = 0.36). The increase in BCDVA post–Nd:YAG laser capsulotomy was significant for the sharp-edged (0.19 D [SD, 0.20 D]) versus the round-edged (0.38 D [SD, 0.30 D]) silicone IOL (p = 0.03) [Table 3]. There were no significant differences between individual IOLs within groups for improvement of BCDVA post–Nd:YAG laser capsulotomy.

Post–Nd:YAG laser capsulotomy, 1 patient had a transient rise in intraocular pressure, which resolved with topical antiglaucoma medications. No other adverse effects from Nd:YAG laser capsulotomy were noted.

Discussion

PCO is the most frequent cause of decrease in visual acuity after cataract surgery.[29] Nd:YAG laser capsulotomy to treat PCO is effective, but is associated with potentially serious complications such as ocular inflammation, cystoid macular oedema, retinal detachment, increased intraocular pressure, and IOL damage.[30, 31]

Several studies have reported that IOL material has a direct relationship to PCO formation, with lower PCO rates found for acrylic IOLs than for silicone or PMMA IOLs.[24, 32] This was postulated to be due to better anterior capsule adherence with the acrylic IOL, which acts as a mechanical barrier and provides less space for lens epithelial cells to grow.[24,33] Hollick et al found considerably higher small-cell and giant-cell counts induced in the foreign-body response for silicone IOLs than for acrylic IOLs.[25] In this study, the mean time to development of visually significant PCO was longer for acrylic IOLs than for silicone IOLs (p = 0.001).

However, this study also found a significant difference in the time to development of PCO for different IOLs made of the same material and optic edge. Among the acrylic IOLs with a sharp edge, Ar40e had the longest time to development of visually significant PCO (53.17 months [SD, 19.88 months]), followed by 1CU and MA60BM, which had similar times to development of visually significant PCO (38.43 months [SD, 8.89 months] and 37.69 months [SD, 19.90 months], respectively). Akreos Adapt had the shortest time to development of visually significant PCO among this group of IOLs (26.91 months [SD, 9.18 months]).

AR40e and MA60BM are both hydrophobic acrylic IOLs, while 1CU and Akreos Adapt are hydrophilic IOLs. Studies by Kugelberg et al[34] and Suh et al[35] found that hydrophilic acrylic IOLs had a significantly greater incidence and severity of PCO than hydrophobic acrylic IOLs. The variation in time to development of visually significant PCO among the different acrylic IOLs in this study suggests that other factors besides optic material and edge, such as hydrophilicity, have an important role to play in the development of PCO.

SA40N had the longest time to development of visually significant PCO amongst the silicone IOLs with a sharp-edge (37.93 months [SD, 20.69 months]), followed by Z9000 (25.14 months [SD, 3.34 months]), and ZM900 (17.93 months [SD, 6.35 months]). SA40N is a silicone 3-piece refractive multifocal IOL, ZM900 is a diffractive IOL, and Z9000 is an aspheric IOL with a modified prolate anterior surface. There have been few studies on the rate of development of PCO for different multifocal IOLs and aspheric IOLs. This study found a significant difference in time to development of PCO between a refractive and diffractive IOL and an aspheric IOL. Further long-term studies are needed to study PCO rates for these IOLs and the impact on visual function.

The mean time interval to development of visually significant PCO for the silicone IOL with a round edge (SI40NB) was the shortest of all the IOLs (16.80 months [SD, 13.07 months]). Buehl et al found that the sharp posterior optic edge of a silicone IOL

significantly reduced PCO development compared with a round posterior optic edge.[19] One possible mechanism is that a barrier effect is created by contact inhibition of migrating lens epithelial cells by the sharp IOL optic edges.[19,27,28,36,37] Peng et al found that, in an IOL with a square edge, there was frequently sudden cessation of cell migration where the peripheral edge of the optic came into contact with the posterior capsule, rendering the posterior capsule relatively cell free.[38]

The decrease in visual acuity with development of PCO was not significant for the lens material, but was significant for the type of lens edge ($p = 0.02$), with a greater mean decrease for the silicone IOL with a round edge (0.29 D [SD, 0.27 D]) than for the silicone IOL with a sharp edge (0.09 D [SD, 0.16 D]). This difference was not significant among the different IOLs within each group. Patients implanted with round-edged silicone IOLs develop PCO at a significantly shorter time from cataract surgery, with a greater impact on visual acuity, than those implanted with sharp-edged silicone IOLs.

There were some limitations to this study, as the design led to unavoidable bias. This was a retrospective study and the lack of randomisation resulted in a disproportionately larger number of patients who received an acrylic IOL with a sharp edge. Many surgeons participated in this study, and IOL preferences and different surgical techniques may have had an impact on PCO development. A prospective randomised study with a longer follow-up period is needed to further assess the differences between the different IOL groups.

The aetiology of PCO has been found to be related to IOL factors such as optic material and optic edge. This study showed that there is variation in the time to development of visually significant PCO after cataract surgery among different IOLs made of the same material and optic edge. This has important implications for the future development of IOLs and for the choice of IOL made by surgeons for their patients.

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Agreement of Perkins Hand-held Applanation Tonometry with Goldmann Slit-lamp Applanation Tonometry

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Aim: To evaluate the agreement of Goldmann slit-lamp applanation tonometry with Perkins hand-held applanation tonometry for measuring intraocular pressure, controlling for central corneal thickness.
Methods: In this prospective study, 109 eyes of 109 patients were included at random. Eyes were excluded if they had undergone intraocular surgery within 3 months of the study or if they had corneal pathology. The right eye was selected by convention unless a patient's right eye fit the exclusion criteria or a patient was monocular.
Results: The mean intraocular pressures measured by Goldmann applanation tonometry and Perkins applanation tonometry were 16.88 mm Hg (SD, 7.38 mm Hg) and 16.77 mm Hg (SD, 7.21 mm Hg), respectively. The mean intraocular pressure difference between the 2 types of tonometry was 0.11 mm Hg (SD, 2.38 mm Hg). The intraocular pressures adjusted for central corneal thickness were 17.52 mm Hg (SD, 7.06 mm Hg) and 17.43 mm Hg (SD, 6.93 mm Hg) for Goldmann applanation tonometry and Perkins applanation tonometry, respectively, with a mean difference of 0.09 mm Hg (SD, 2.41 mm Hg). Age, ethnicity, sex, time of day, glaucoma type, number of medications, type of medication, prior surgery, and central corneal thickness did not have a significant effect on intraocular pressure measurement differences between Goldmann and Perkins applanation tonometry ($p > 0.05$). There was high correlation between Goldmann and Perkins applanation tonometry by Pearson correlation ($\chi^2 = 0.95$) and intra-class correlation ($R^2 = 0.98$; $p < 0.0001$).
Conclusions: Goldmann slit-lamp applanation tonometry and Perkins hand-held applanation tonometry are comparable ($p = 0.48$) and can be used interchangeably. Central corneal thickness, demographics, and other ocular factors did not appear to have any significant effect on differences between the 2 devices.

Key words: Cornea, Glaucoma, Intraocular pressure, Tonometry, ocular

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Introduction

Glaucoma is the most common cause of blindness in the world, second only to cataracts.[1] There is a direct correlation between intraocular pressure (IOP) and the progression and severity of optic nerve damage.[2,3] As IOP is the only treatable risk factor in glaucoma, the accuracy of the measurements is paramount.

Currently, the gold standard for measuring IOP is the Goldmann applanation tonometer (GAT). The Goldmann applanator is mounted on a slit lamp, and the IOP is measured with the patient sitting in the upright position. The mechanism of GAT is based on the Imbert-Fick principle, in which the magnitude of force (the biprism tip) against a sphere (the eye) equals the pressure within the sphere times the area flattened (3.06 mm^2 of the cornea) by the force.[4,5] The main drawback of GAT is availability, as many institutions do not have a slit lamp. In addition, patients must be able to assume an upright position. This may be difficult or impossible for young children, individuals who are confined to bed or have altered levels of consciousness, and in the operating room.

Although various portable hand-held devices such as the TonoPen and Schiotz tonometer are available, the Perkins applanation tonometer (PAT) is the most similar to the GAT in its design and mechanism. Like the GAT, the PAT is based on the Imbert-Fick principle, with the same measurement over an area of 3.06 mm^2 of cornea. Several studies of the hand-held PAT have assessed its

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accuracy since its conception in 1956.[5-8] However, central corneal thickness (CCT) and intra-class correlation were not taken into consideration in these studies.

The purpose of this study was to ascertain the equivalence of IOP measurements by the PAT and GAT, controlling for the effect of CCT and demographic variables. Specifically, the strength of association and the agreement of IOP measurements by the PAT and GAT were measured.

Methods

Patients

109 eyes of 109 participants were included in this prospective study. All measurements were performed at Loma Linda University Medical Center and Riverside County Regional Medical Center, Loma Linda, USA, during routine clinic visits from January 2006 to April 2006. Approval from the Institutional Review Board of Loma Linda University was obtained prior to the start of the study.

Participants were selected at random, irrespective of their glaucoma diagnosis. The exclusion criteria for the study were the presence of corneal pathology or intraocular surgery within 3 months of the study. The right eye was selected by convention unless a patient's right eye fit the exclusion criteria or a patient was monocular.

Design

Patients' demographics (age, race, sex, and glaucoma diagnosis), CCT measured by an ultrasonic pachymeter (Sonomed 200P; Sonomed Inc, Lake Success, USA), ocular medications, prior ocular surgeries, type of lens, and time of applanation were recorded.

Prior to each IOP measurement, the biprism tips of the GAT and PAT were sterilised. One drop of fluorescein sodium and benoxinate hydrochloride ophthalmic solution (Fluress®; Akorn Inc. Buffalo Grove, USA) was instilled in each eye, and the patient was seated comfortably. Close attention was paid to the appearance of the fluorescein rings to achieve ideal tonometer-tear contact, as outlined by Whitacre and Stein.[4] Fluorescein ring thickness was approximated to one-third of the radius of the fluorescein-free central zone, and fluorescein was added or blotted away as needed. IOP measurements were randomised to be either first by slit-lamp GAT followed by hand-held PAT or vice versa. Patients were assigned the order of measurements prior to examination, and the order was blinded to the investigators, except to the clinician performing the measurements. All measurements were performed by 1 clinician. A single measurement from each instrument was recorded, along with the time at which the procedure was performed. During each PAT measurement, the patient assumed the upright position. Patients were instructed to relax, to refrain from lid squeezing, and to breathe normally prior to each IOP measurement. The eyelid was retracted manually, and care was taken not to apply any pressure on the globe to prevent false elevation of IOP. All IOP values were rounded up to the nearest whole number.

Statistical Analysis

Descriptive statistics were used to profile the demographic data and population characteristics. Missing data were not imputed. Pearson correlation, Bland-Altman method, and intra-class correlation were used to determine significant differences in these variables within the study population. Statistical significance was defined as $p < 0.05$. The Pearson correlation measured the strength of association between the GAT and PAT IOP, but did not analyse the agreeability of the 2 instrument measurements. A device whose measurement is systematically deviated by a certain amount from another measuring device can have a strong linear relationship, but have poor agreement. As it is unlikely that 2 different instruments will agree completely by giving exactly the same measured values on every measurement, intra-class correlation determines how different measurements can be and still remain agreeable. Intra-class correlation investigates measurement error against the true value, and also tests repeatability by comparing differences from the mean.[9] This study used intra-class correlation to assess the reliability between GAT and PAT. The Bland-Altman method was then used to measure the agreeability.[9] Pair-wise *t* test of the IOP measurements for each patient was performed.

Results

The mean IOPs for the 109 eyes by GAT and PAT were 16.88 mm Hg (SD, 7.38 mm Hg; range, 5-54 mm Hg) and 16.77 mm Hg (SD, 7.21 mm Hg; range, 4-55 mm Hg), respectively. The mean difference in IOP was 0.11 mm Hg (SD, 2.38 mm Hg). The mean CCT was 538 μm (SD, 44 μm; range, 436-699 μm). IOP was adjusted for CCT according to the nomogram by Doughty and Zamen.[10] The adjusted IOPs were 17.52 mm Hg (SD, 7.06 mm Hg; range, 6-50 mm Hg) and 17.43 mm Hg (SD, 6.93 mm Hg; range, 5-51 mm Hg) for GAT and PAT, respectively, with an average difference of 0.09 mm Hg (SD, 2.41 mm Hg; range, -5-13 mm Hg).

The demographic data and population characteristics are shown in Table 1. Intra-class correlation for the GAT and PAT IOP measurements had high agreement, as shown in Figure 1.

Demographic factors, time of day, glaucoma type, number of medications, type of medication, prior surgery, and CCT did not have a significant effect on IOP differences, using analysis of covariance with CCT as a covariate, between GAT and PAT ($p > 0.05$). The correlation coefficient ($\chi^2 = 0.95$, $p < 0.0001$) was significantly

Table 1. Patients' demographics (n = 109).

Parameter	Number of patients (%)	Mean (SD)
Age (years)		60.04 (20.41)
Age group (years)		
<50	25 (22.9)	
50-70	42 (38.5)	
>70	42 (38.5)	
Sex		
Male	57 (52.3)	
Female	52 (47.7)	
Ethnicity		
Caucasian	32 (29.4)	
Black	18 (16.5)	
Hispanic	46 (42.2)	
Asian	12 (11.0)	
Other	1 (0.9)	
Eye		
Right	87 (79.8)	
Left	22 (20.2)	
Number of medications		2 (1.7)
0	39 (36.5)	
1	14 (13.1)	
2	8 (7.5)	
3	16 (15.0)	
4	29 (27.1)	
5	1 (0.9)	
Type of medication		
Prostaglandin agonist	57 (52.3)	
β-Blocker	51 (46.8)	
Carbonic anhydrase inhibitor (topical)	47 (43.1)	
α-Agonist	41 (37.6)	
Carbonic anhydrase inhibitor (oral)	3 (2.8)	
Diagnosis		
Primary open angle	45 (41.3)	
Suspect	13 (11.9)	
Chronic angle closure	12 (11.0)	
No glaucoma	11 (10.1)	
Normal tension*	9 (8.3)	
Neovascular	9 (8.3)	
Combined mechanism	4 (3.7)	
Pseudoexfoliation	2 (1.8)	
Angle recession	1 (0.9)	
Pigmentary dispersion syndrome	1 (0.9)	
Uveitic	1 (0.9)	
Congenital	1 (0.9)	
Lens status		
Phakic	86 (82.7)	
Pseudophakic	16 (15.4)	
Aphakic	2 (1.9)	
Prior intraocular surgery		33 (30.2)
Cataract extraction	17 (15.6)	
Trabeculectomy	11 (10.1)	
Pars plana vitrectomy	3 (2.8)	
Glaucoma drainage device	2 (1.8)	

* Normal tension glaucoma was defined as glaucomatous damage at IOP <21 mm Hg after having ruled out other aetiologies of vision loss or cupping.

different from 0 between the 2 tonometry methods using Pearson correlation and intra-class correlation ($R^2 = 0.98$, $p < 0.0001$). The IOP measurements were similar between the GAT and PAT, being within ±1 mm Hg 63% of the time and within ±2 mm Hg 79% of the time (Figure 2). Paired *t* test showed no significant difference between the 2 measurements ($p = 0.6276$).

Discussion

Since its introduction in 1965, the PAT has proven itself to be an accurate means of measuring IOP, especially in settings in which the GAT is not available.[5,7,8] In 1969, Whitty found that the PAT provided a lower IOP measurement than the GAT, with a difference of 1.0 to 1.5 mm Hg, which was thought to be acceptable.[11] In this study, the results were reliable for both techniques, with a mean difference of 0.11 mm Hg (SD, 2.38 mm Hg) between PAT and GAT, which was 0.09 mm Hg (SD, 2.41 mm Hg) when corrected for CCT. Besides the PAT, other portable tonometry devices such as the TonoPen have been commonly used. The TonoPen has an advantage over applanation tonometry because of its ability to measure IOP in patients with irregular or scarred corneas.[12,13] However, recent studies have shown the TonoPen to underestimate IOP, particularly at higher levels.[14-16] Although the TonoPen and the PAT have parallel accuracies, the PAT may have less variability as it operates on the same principal as GAT.[15]

CCT has been shown to significantly alter measured IOP in GAT.[10,17,18] It is common practice to adjust the IOP according to CCT using the nomogram by Doughty and Zamen.[10] However, no study has shown the effects of CCT on IOP for PAT. It would be expected that CCT would have the same effect on PAT as on GAT, given that they function according to the same mechanism. In this study, CCT did not appear to have any significant effect on the differences between the 2 devices.

Although the mechanism of PAT is similar to that of GAT and PAT has been shown in this study to mirror the accuracy of GAT, there are other factors that influence IOP measurements. Lid squeezing and factors that increase venous pressure — Valsalva manoeuvres, breath holding, and wearing tight clothing — are common patient-dependent variables that lead to overestimation of IOP measurement.[4] Therefore, it is important to ensure that patients are comfortable, and to encourage normal breathing and eyelid relaxation. Other factors affecting IOP measurements include corneal abnormalities, corneal thickness, astigmatism, and decreased fluorescence of the precorneal tear film.[4] Decreased fluorescence can prove to be a problem for PAT due to its smaller light source. Compared with GAT, it is harder to visualise the fluorescein half-rings with PAT.[4,8] However, measures to decrease ambient light can help to compensate for this deficiency.

In an earlier study, dos Santos et al demonstrated that patients with a higher body mass index (BMI) have a greater potential for increased anxiety, and Valsalva and muscle contractions due to positioning difficulty and discomfort.[8] In addition, the spatial

Figure 1. Bland-Altman plot of intraocular pressure differences for the Goldmann and Perkins applanation tonometers from the mean intraocular pressure. The horizontal lines depict 2 SD above and below the mean with a 95% confidence level.

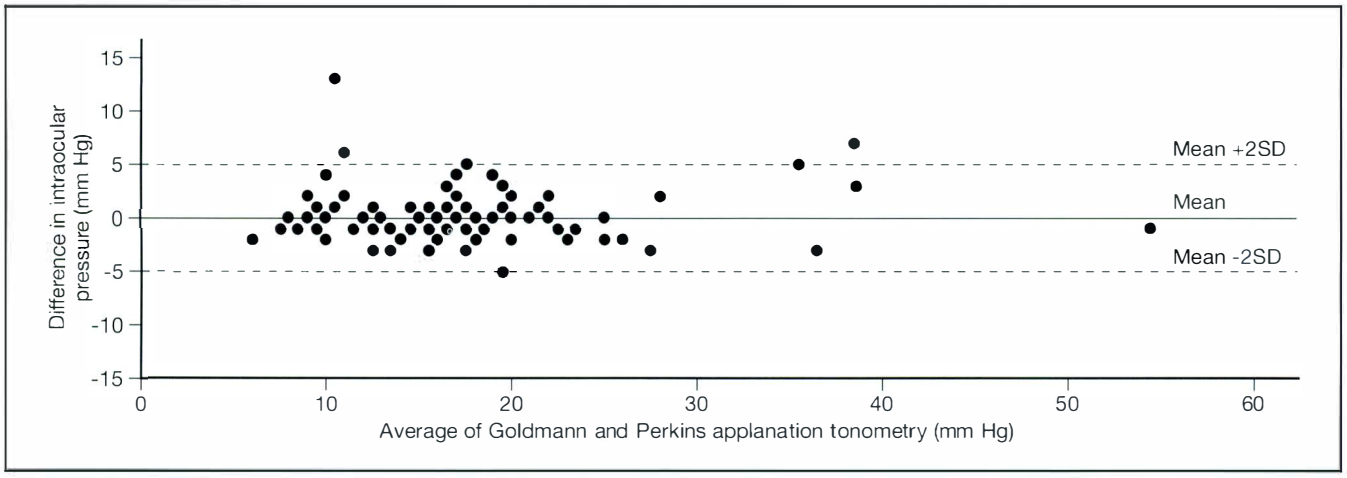
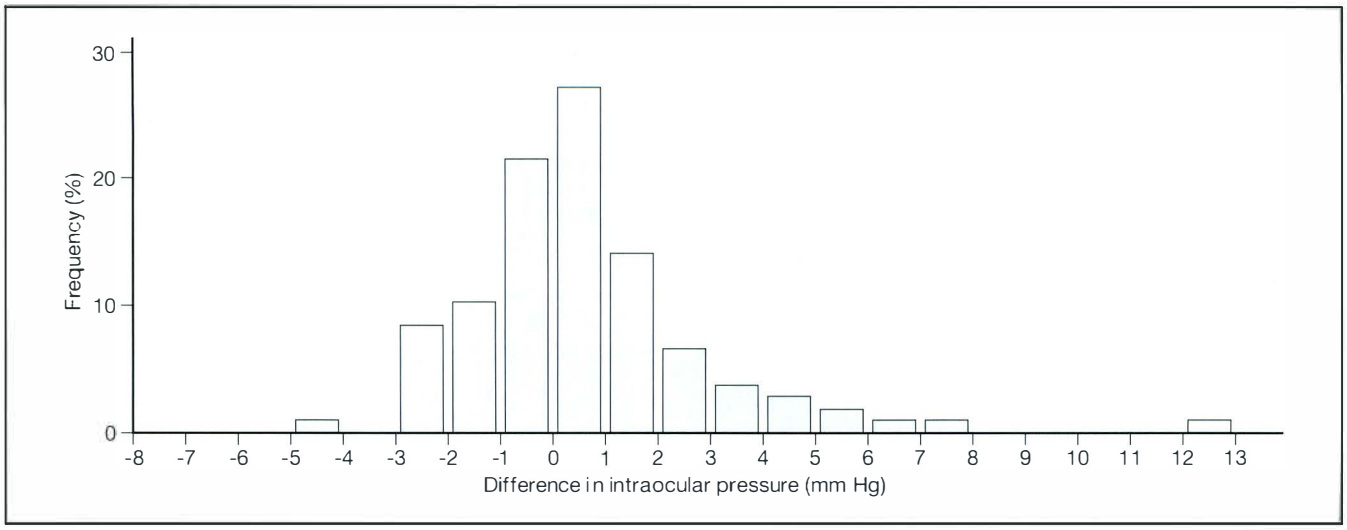


Figure 2. The frequency and magnitude of intraocular pressure differences between Goldmann and Perkins applanation tonometry measurements.



limitations of larger individuals can induce possible compression of the chest and abdomen against the slit lamp, thus increasing the measured IOP by GAT. These researchers concluded that PAT may be helpful for minimising falsely elevated IOP measurement in patients with higher BMI by avoiding the factors listed above. BMI was not recorded in this study. Dos Santos et al[8] had assumed that GAT and PAT were agreeable/interchangeable given the reproducibility from their study and from that of Whitacre and Stein.[4] However, the data were not subjected to intra-class correlation or Altman-Bland analysis.

All PAT measurements in this study were performed with the patient in the upright position. The use of PAT as a portable applanation device can extend beyond clinic use to patients in the operating room or to those who are confined to bed. It is likely that measuring IOP with patients in various positions will occur. In the study by Whitty, there appeared to be no difference in hand-held applanation tonometry measurements taken in the lying or sitting position.[11] However, variations in patients' postures have been shown to have an effect on IOP in recent studies.[19] By including serial measurements of IOP using the PAT with the patient in the standing, sitting, and supine positions, and by utilising intra-class correlation, a more accurate assessment of the variability in PAT measurements with regards to posture may be obtained.

In an attempt to minimise technical measurement variability, one clinician was chosen to perform all measurements in this study. However, this could introduce measurement bias. In addition, multiple measurements of each type of applanation tonometry could have increased the accuracy of the measurements. Inclusion of a control group with repeated measurements would have added to the strength of the study by demonstrating reproducibility in the measurements with each of the applanation devices by the observer.

The PAT is a reliable alternative when it is not possible to perform GAT, as demonstrated by high intra-class correlation. As with the GAT, the PAT requires the same precautionary measures to minimise measured IOP deviations from the true IOP. Further investigation is needed to analyse the effect of posture on PAT measurements.

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Estimated Prevalence of Normal Tension Glaucoma Using the Non-mydriatic Fundus Camera as a Screening Tool in Korean Adults

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Aim: *To evaluate the prevalence and the characteristics of glaucoma in the Korean population by using a non-mydriatic fundus camera.*
Methods: *16,107 people were enrolled in a glaucoma screening programme. Screening tests included intraocular pressure measurement by non-contact tonometry and fundus photography using a non-mydriatic fundus camera. 731 participants were referred for diagnostic glaucoma examination, and 306 of these participants completed comprehensive glaucoma evaluation, which included applanation tonometry, gonioscopy, stereoscopic disc photography, retinal nerve fibre layer photography, and standard automated perimetry.*
Results: *Of the 306 participants who completed the comprehensive glaucoma investigation, 116 were diagnosed with normal tension glaucoma, 10 had primary open angle glaucoma, and 21 had ocular hypertension. After stratification and direct standardisation by age and sex, the estimated prevalence of normal tension glaucoma among the 16,107 participants was 2.0%, while the prevalences of primary open angle glaucoma and ocular hypertension were 0.2% and 0.4%, respectively.*
Conclusion: *The prevalence of glaucoma was determined to be 2.2% in the Korean population, 89.0% of which was attributable to normal tension glaucoma.*

Key words: *Glaucoma, Korea, Prevalence*

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Introduction

Glaucoma is a leading cause of irreversible blindness in many populations. The prevalence of glaucoma has been reported to range from 0.5% to 8.5%.[1-13] Racial variations in prevalence have been reported, for example, open angle glaucoma is more frequent among people of West African descent[7] and angle closure glaucoma (ACG) is more frequent in the Inuit population.[14] According to 2 recent reports,[12,13] normal tension glaucoma (NTG) is the most common type of glaucoma in the Japanese population, which suggests a high prevalence of NTG in the populations of East Asia.

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Non-stereoscopic colour 45° retinal images taken by a non-mydriatic digital camera are now widely used for the screening and detection of various ocular diseases such as diabetic retinopathy[15,16] and age-related macular degeneration, because of the convenience and proven acceptability of this technique.[17,18] This study was performed to assess the prevalence and characteristics of glaucoma in the Korean population using non-mydriatic fundus photography as a screening tool.

Methods

Patients

This was a clinic-based study involving 16,107 participants aged 40 years or older who visited the Seoul National University Hospital Health Care System Gangnam Center, Seoul, Korea, for a general health check from June 2003 to December 2005. Institutional

Review Board approval was obtained from Seoul National University Hospital Clinical Research Institute.

Design

Screening examinations for glaucoma included intraocular pressure (IOP) measurement with a non-contact tonometer (CT-60NCT; Topocon, Tokyo, Japan) and fundus photography using a 45° digital non-mydriatic fundus camera (Canon EOS D60; Canon Inc, Utsunomiya, Japan).

Three glaucoma specialists independently evaluated the colour fundus photographs to check for suspicious findings such as glaucomatous optic disc appearance or nerve fibre layer defect. The criteria for suspicious findings were as follows:

- disc suspect — cup-disc ratio (CDR) of the optic disc ≥0.5, CDR asymmetry ≥0.2, vertical cupping of the optic disc, rim width at superior position (11 to 1 o'clock) or inferior position (5 to 7 o'clock) of ≤0.2 of the disc diameter, or disc haemorrhage
- retinal nerve fibre layer (RNFL) suspect — RNFL defects with a width at the disc edge larger than a major retinal vessel, diverging in an arcuate or wedge shape
- IOP ≥22 mm Hg.

All participants with findings suspicious of glaucoma were offered a comprehensive glaucoma evaluation, including Goldmann applanation tonometry, Goldmann 3-mirror gonioscopy, stereoscopic disc photographs, red-free RNFL photography (CF-60Uvi; Canon Inc, Utsunomiya, Japan), and standard automated perimetry (Humphrey Field Analyzer; Allergan Humphrey, San Leandro, USA). The participants received a diagnosis of glaucoma based on optic disc appearance, including CDR, rim width, RNFL defects, visual field examination results, and clinical records obtained during screening and examination.

NTG was defined as IOP ≤21 mm Hg by Goldmann applanation tonometry with open anterior chamber angles by gonioscopy, typical features of a glaucomatous optic disc and RNFL defects, and visual field defects corresponding to optic disc changes. Primary open angle glaucoma (POAG) was defined as IOP >21 mm Hg with open anterior chamber angles, typical features of glaucomatous optic disc and RNFL defects, and visual field defects corresponding to optic disc changes. Ocular hypertension (OH) was defined as IOP >21 mm Hg without evidence of optic nerve damage or visual field abnormalities characteristic of glaucoma. ACG was defined as gonioscopic findings of a narrow angle, where the posterior, usually pigmented, trabecular meshwork was not visible for ≥270° and/or presence of primary peripheral anterior synechiae, IOP >21 mm Hg, and glaucomatous defects to the optic disc, RNFL, and visual field.

Comparisons of parameters among the groups were made by Student *t* test or non-parametric Mann-Whitney test using the Statistical Package for the Social Sciences version 11.0. The prevalence of glaucoma was calculated for different age and sex groups by assuming that prevalences in participants and non-participants were equal. Prevalence rates were estimated in each age group by direct age standardisation of the 16,107 participants who underwent screening.

Table 1. Age and sex distribution of the 16,107 participants who underwent glaucoma screening.

Age group (years)	Participants (n = 16,107)		
	Men	Women	Total
40-49	3525	2892	6417
50-59	3201	2741	5942
60-69	1779	1293	3072
>70	409	267	676
Total	8914	7193	16107

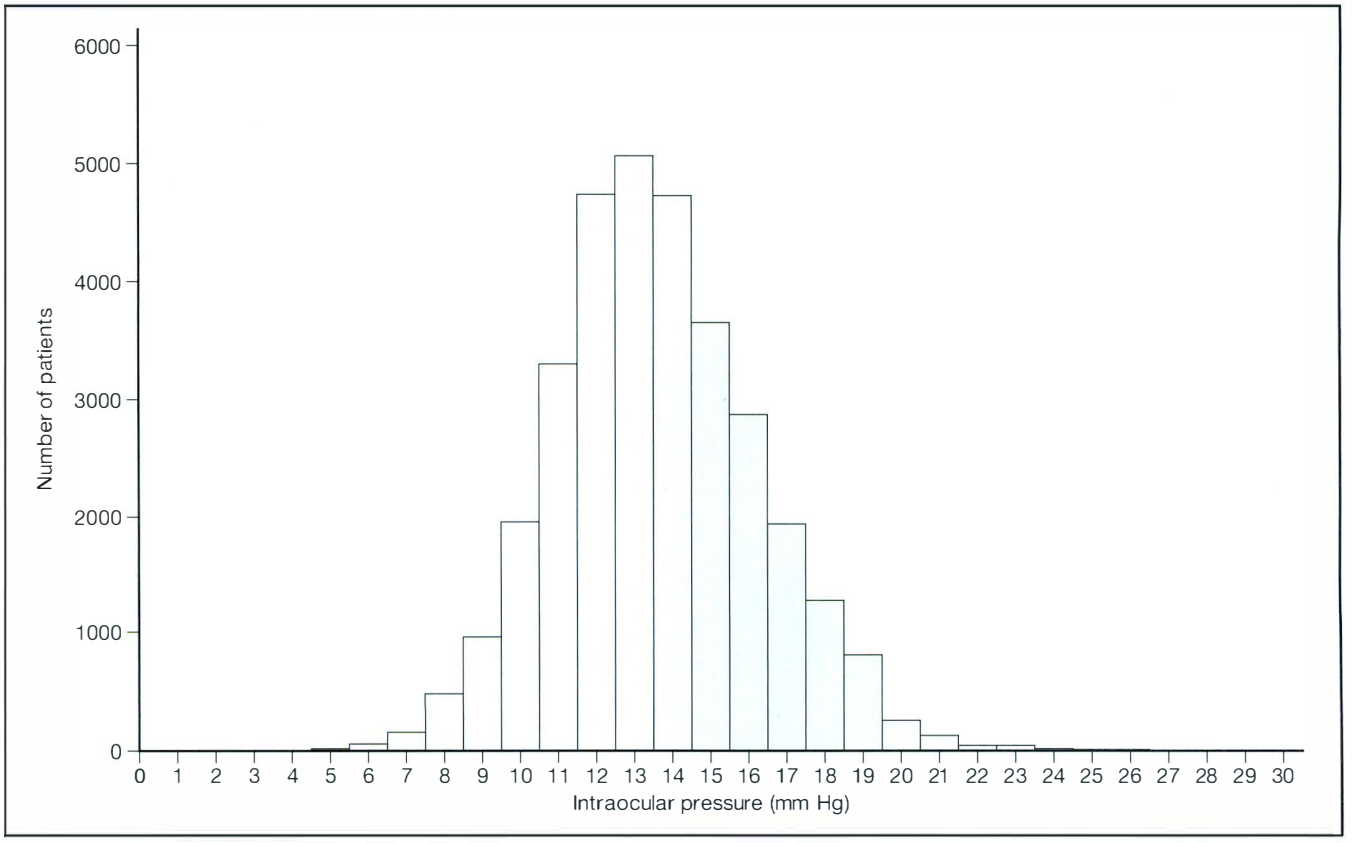
Results

16,107 participants underwent screening; the age and sex distribution of the participants is shown in Table 1. Of these, 731 were referred for further diagnostic examination. According to non-mydriatic fundus photography, 467 participants (2.9% of the 16,107 study population; 63.9% of the 731 glaucoma suspects) were disc suspects and 208 (1.3% of the study population; 28.5% of the glaucoma suspects) were RNFL suspects. Eighty five participants (0.5% of the study population; 11.6% of the glaucoma suspects) had an IOP ≥22 mm Hg, and a normal disc and RNFL appearance. Twenty participants (0.1% of the study population; 2.7% of the glaucoma suspects) had a disc haemorrhage and 2 participants (0.01% of the study population; 0.3% of the glaucoma suspects) had an optic pit.

The mean IOP for the study participants, measured by non-contact tonometry, was 13.6 mm Hg (SD, 2.7 mm Hg); the distribution is shown in Figure 1. There were no significant differences in IOP across sex and/or eye laterality, but IOP tended to decrease with age. The mean IOP was significantly higher in the 40 to 49 years age group than in the 60 to 69 years ($p = 0.006$) and 70 years and older ($p = 0.002$) age groups. The mean IOP in the 50 to 59 years age group was also significantly greater than in the 60 to 69 years ($p = 0.001$) and the 70 years and older ($p < 0.001$) age groups.

Of the 731 glaucoma suspects who were offered further diagnostic examination, 306 participants (41.9%) completed a comprehensive glaucoma evaluation; demographic data for these 2 groups are shown in Table 2. The participation rate was similar for all age and sex groups. Of the 306 participants who completed a comprehensive glaucoma evaluation, 116 had NTG, 10 had POAG, and 21 had OH. ACG was diagnosed in 2 patients. Figure 2 shows a patient with NTG diagnosed by red-free RNFL photography and standard automated perimetry after referral for a suspicious RNFL defect by non-mydriatic colour fundus photography.

Figure 1. Distribution of intraocular pressure measured by non-contact tonometry among 16,107 participants who underwent glaucoma screening. A Gaussian normal distribution was observed, with a mean intraocular pressure of 13.6 mm Hg (SD, 2.7 mm Hg).



To evaluate the ability of the non-mydriatic fundus camera to detect a glaucomatous disc or RNFL changes, the percentage of participants who had a suspicious disc or RNFL changes by non-mydriatic colour fundus photography, and were confirmed to have glaucoma in the subsequent glaucoma evaluation, were analysed. Of 289 participants who completed the subsequent glaucoma evaluation after abnormal disc or RNFL findings by non-mydriatic fundus photography, 123 (42.6%) were diagnosed with glaucoma (NTG or POAG). After stratification by age and direct standardisation based on the assumption that prevalences in participants and non-participants were equal, the estimated prevalence of NTG among the 16,107 study participants was 2.0%, and the prevalences of POAG and OH were 0.2% and 0.4%, respectively. The prevalence of NTG increased with increasing age (Table 3 and Figure 3). The estimated prevalences of glaucoma in the different age groups were 1.6% in the 40 to 49 years age group, 2.3% in the 50 to 59 years age group, 2.7% in the 60 to 69 years age group, and 5.3% in the 70 years and older age group.

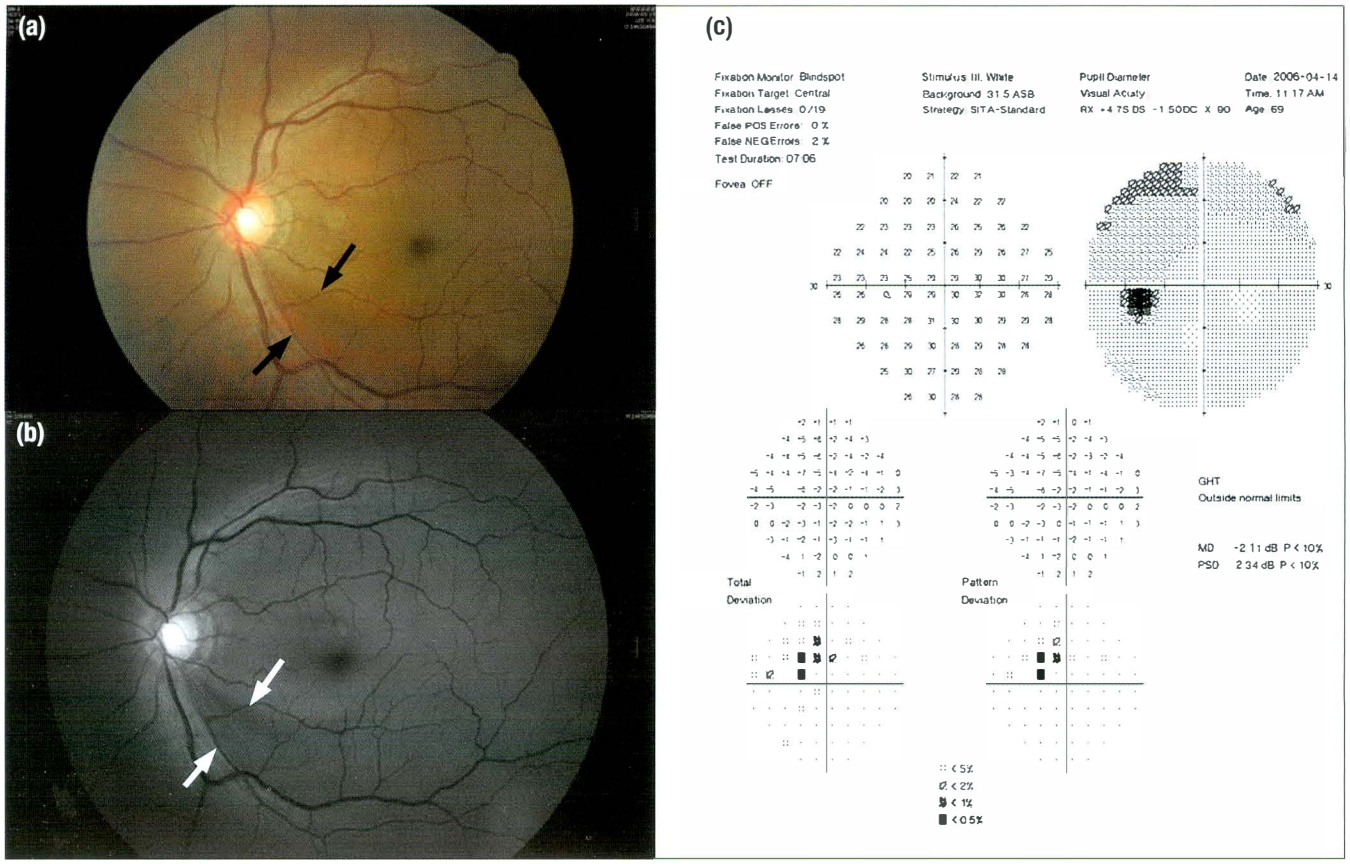
Discussion

This study enrolled individuals who attended the Seoul National University Hospital Health Care System Gangnam Center for a general health check. Therefore, this was a randomly selected population, although it did not represent the whole Korean population. The prevalence of glaucoma in this population was 2.2%, and 89.0% of the population with glaucoma had NTG. This finding is comparable with those of 2 previous studies in the Japanese population.[12,13] The study conducted by Shiose et al between 1988 and 1989 found an

Table 2. Age and sex distribution of participants who underwent glaucoma evaluation (participants) and those who were referred for glaucoma evaluation (glaucoma suspects).

Age group (years)	Participants (n = 306)			Glaucoma suspects (n = 731)		
	Men	Women	Total	Men	Women	Total
40-49	60	48	108	140	89	229
50-59	66	50	116	170	101	271
60-69	41	27	68	118	57	175
>70	10	4	14	35	21	56
Total	177	129	306	463	268	731

Figure 2. A patient with normal tension glaucoma diagnosed after referral for a suspicious retinal nerve fibre layer defect by non-mydriatic colour fundus photography. (a) Non-mydriatic fundus photograph showing retinal nerve fibre layer defects (arrows) in the inferotemporal portion; (b) red-free retinal nerve fibre layer photograph showing a wedge-shaped retinal nerve fibre layer defect (arrows) in the inferotemporal portion; and (c) standard automated perimetry showing an arcuate defect in the superior portion.



NTG prevalence of 2.04% and a POAG prevalence of 0.58%.[12] The study by Iwase et al performed between 2000 and 2001 showed that Japanese people have a high prevalence of OAG (3.9%), of which 92.0% was attributable to NTG.[13] In the Korean population, 2 screening studies found that 1.71% and 2.04% of the participants had NTG and 0.20% and 0.23% had POAG.[19,20]

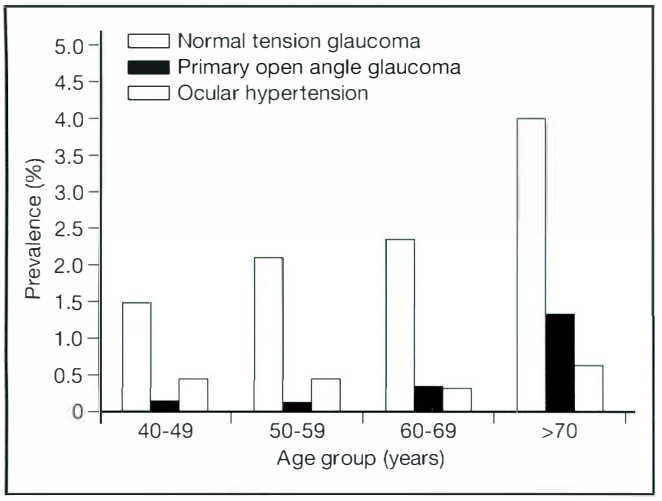
The differences between this study and the previous studies in the Korean population[19,20] are 3-fold. First, this study included more than 3.5 times the number of participants than the previous studies. Second, this study used a non-mydriatic fundus camera to screen for glaucoma, which was capable of photographing the posterior pole of the retina sufficiently to show an RNFL defect as well as the optic disc, whereas the previous studies used direct ophthalmoscopy or disc photography, capable of showing only the optic disc. RNFL defect is an important finding for early detection of glaucoma, because it is known to develop in glaucoma before optic disc changes occur. By using non-mydriatic colour fundus photography, RNFL defects were assessed for glaucoma screening, although the resolution for RNFL thickness studies is not as good as for other imaging devices. Third, whereas the previous studies used

Table 3. Estimated prevalence of normal tension glaucoma by age and sex.

Age group (years)	Men			Women		
	Number of patients		Estimated prevalence (95% confidence interval) [%]	Number of patients		Estimated prevalence (95% confidence interval) [%]
	Observed	Adjusted*		Observed	Adjusted*	
40-49	23/60	53.7/3525	1.5 (1.0-2.3)	20/48	37.1/2892	1.3 (0.8-2.0)
50-59	29/66	74.7/3201	2.3 (1.6-3.3)	23/50	46.5/2741	1.7 (1.1-2.5)
60-69	16/41	46.1/1779	2.6 (1.5-4.2)	10/27	21.1/1293	1.7 (0.8-3.0)
>70	4/10	14.0/409	3.4 (0.9-8.7)	2/4	10.5/267	3.9 (0.0-5.6)
Total	72/177	188.5/8914	2.1 (1.7-2.7)	55/129	115.2/7193	1.6 (1.2-2.1)

* The prevalence rate was calculated in each age and sex group assuming that the rates for participants and non-participants were equal. The overall prevalence rates were standardised to the age distribution of the participants who underwent glaucoma screening at the Seoul National University Healthcare System Gangnam Center.

Figure 3. The estimated prevalence of glaucoma by age.



only visual field examination to definitively diagnose glaucoma, in this study, RNFL photography was performed in addition to visual field examination, making earlier detection of glaucoma possible. However, direct comparisons between the present and previous surveys are difficult because the diagnostic criteria used and the study populations differ. Nevertheless, the findings suggest that the prevalence of NTG is higher in East Asian populations than in Caucasian populations, whereas the prevalence of POAG is higher in Caucasian populations.[12,13,19,20]

One notable feature of this study was the use of a non-mydriatic fundus camera as a screening tool for glaucoma. This camera uses an infrared light to show the fundus through a dark-adapted pupil. The advantages of this camera versus the standard 30° film-based camera is that it is less expensive, has a shorter learning curve, and provides excellent resolution and images that can be easily magnified and further manipulated. In addition, it is unnecessary to pharmacologically dilate the pupils, circumventing the risk of an acute angle closure attack. According to Shiose et al, disc appearance is more important than IOP measurement for glaucoma screening, especially in East Asian populations with a high prevalence of NTG.[12] Using non-mydriatic fundus photography, it was possible to detect abnormal optic disc and suspicious RNFL defect findings; 42.6% of participants who completed a full glaucoma evaluation after suspect optic disc or RNFL findings on non-mydriatic fundus photography were diagnosed with glaucoma.

This study has several limitations. First, only 41.9% of participants who were suspected to have glaucoma after screening completed a full glaucoma evaluation. It is possible that this may have influenced the accuracy of the results regarding the true prevalence of glaucoma. Second, IOP was measured once during screening, using a non-contact tonometer with the associated possible lack of accuracy. This could result in overdiagnosis of NTG, although the definitive diagnosis of NTG or POAG was based on diurnal IOP measurements with Goldmann applanation tonometry during the glaucoma evaluation of glaucoma suspects. It is possible that the IOP cut-off criterion of 21 mm Hg for screening could have led to patients with ocular hypotension being overlooked. Third, the angle was not evaluated during screening, which may explain why only 2 patients were diagnosed with ACG. In addition, central corneal thickness, which is known to affect the measurement of true IOP,[21,22] was not measured. Finally, there were a relatively low number of participants older than 70 years (4.2% of participants who underwent screening) compared with the general Korean population (13.6%). This could have resulted in underestimation of the prevalence of glaucoma because glaucoma is usually found to be more prevalent in older populations.

The overall prevalence of glaucoma in the Korean population was estimated to be 2.2%, and NTG accounted for 89.0% of all glaucoma.

Acknowledgement

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Late Complications of Primary Trabeculectomy with Different Concentrations of Mitomycin C

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Aim: *To determine the late complications of trabeculectomy with different concentrations of mitomycin C for patients with glaucoma.*
Methods: *The medical records of patients with primary glaucoma who underwent primary trabeculectomy with mitomycin C 0.4 mg/mL or 0.2 mg/mL from January 1997 to December 2003 were retrospectively reviewed. The main outcome was late postoperative complications, which was defined as complications occurring at or after 3 months. Other outcome measures were intraocular pressure reduction, number of antiglaucoma medications, and surgical success. Patients were followed up for 2 years.*
Results: *165 eyes of 141 patients were enrolled in the study. No statistical difference in late complications was found between the mitomycin C 0.4 mg/mL group and 0.2 mg/mL group. Serious complications of blebitis or bleb-related endophthalmitis were low. There was a statistically significant difference between preoperative and postoperative intraocular pressure reduction within each group. The median number of postoperative antiglaucoma medications was similar for both groups. After 2 years, the mitomycin C 0.4 mg/mL group had a 65% complete success rate and 31% qualified success rate, whereas the mitomycin C 0.2 mg/mL group had a 44% complete success rate and a 42% qualified success rate.*
Conclusions: *Mitomycin C 0.4 mg/mL was not associated with more complications than mitomycin C 0.2 mg/mL in clinical practice. Although the overall success rate was not as high for mitomycin C 0.2 mg/mL as for mitomycin C 0.4 mg/mL, mitomycin C 0.2 mg/mL was effective for controlling intraocular pressure.*

Key words: *Antineoplastic agents, Postoperative complications, Trabeculectomy*

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Introduction

Trabeculectomy has been the surgical procedure of choice for patients with glaucoma for many decades. This widely-accepted surgery has advantages for patients with glaucoma for whom medications have failed to control the intraocular pressure (IOP) or halt disease progression. However, long-term IOP control cannot be achieved with trabeculectomy alone due to scarring of the filtering bleb, which is the most common cause of surgical failure.[1-4]

Mitomycin C (MMC), an antineoplastic agent, has been introduced as an adjunctive treatment with trabeculectomy to inhibit wound healing and reduce bleb fibrosis, thereby improving the overall success rates, which vary from 66% to more than 90%.[5] However, MMC application in primary trabeculectomy can cause serious complications such as hypotony, bleb leak, shallow or flat anterior chamber, blebitis, and bleb-related endophthalmitis.

The most commonly used MMC concentrations ranges from 0.2 mg/mL to 0.5 mg/mL for an average exposure of 2 to 5 minutes. Many studies have been performed to define the optimal concentration and application duration that will provide the most benefit and least complications.[6-9] To date, there has been no conclusive evidence for the ideal concentration and exposure time for MMC. Currently, its use is based on an individual's glaucoma condition and the surgeon's preference. Although MMC 0.2 mg/mL and 0.4 mg/mL are the most commonly used concentrations at the Department of Ophthalmology, Chulalongkorn University, Bangkok, Thailand, doubt remains about whether the outcomes differ in clinical practice.

As a number of studies have shown varying success rates for trabeculectomy with MMC, it may be that the effect is different in an Asian population, especially Thai, than in a Caucasian population.

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This study was performed to assess the long-term safety profile of trabeculectomy with MMC 0.2 mg/mL and 0.4 mg/mL, with particular reference to late complications.

Methods

Patients

The medical records of all patients with primary glaucoma, either open angle or angle closure, who underwent primary trabeculectomy with MMC 0.4 mg/mL (January 1997 to December 2001) or MMC 0.2 mg/mL (January 2002 to December 2003) were reviewed. All patients attended regular follow-up for 2 years postoperatively, at 1 day, 2 weeks, and 1, 3, 6, 12, and 24 months. Patients with secondary glaucoma or congenital or developmental glaucoma, previous intraocular surgery or laser treatment within 3 months of trabeculectomy, or uncontrolled systemic disease were not recruited. The following information was recorded for all patients included in the study: sex, age, glaucoma diagnosis, visual acuity, preoperative IOP, preoperative use of antiglaucoma medication, and lens status.

The study was approved by the institutional ethics committee of the hospital. Informed consent for surgery was obtained from all patients prior to the operation. All surgeries were performed by the hospital staff, glaucoma fellows, and residents under supervision. Permission from the hospital director for patients' data acquisition was obtained.

Design

The main outcome measure was late postoperative complications, defined as complications that occurred at or after 3 months postoperatively. The follow-up period was 2 years after operation. Complications that occurred from 3 months to 2 years were classified as late complications.

Bleb leakage was documented if there was a visible sign or positive Siedel's test for constant aqueous leak from a particular site of the surgical bleb area. Shallow anterior chamber depth (ACD) was considered if the peripheral ACD was only slit deep or the peripheral iris was in contact with the posterior cornea, while the central ACD was formed or shallow, but there was no lens-corneal touch. Flat ACD was defined as no visible ACD requiring urgent intervention. IOP <8 mm Hg was defined as hypotony. Blebitis was recorded if there were signs of infection, such as injected bleb with exudates in the bleb area without inflammatory cells in the anterior chamber. If there were signs of blebitis as well as an inflammatory reaction in the anterior and/or posterior segment, bleb-related endophthalmitis was documented.

For the analysis of the success rate for control of IOP — the secondary outcome — complete success was defined as an IOP between 8 and 21 mm Hg without any antiglaucoma medications and qualified success was defined as an IOP between 8 and 21 mm Hg with antiglaucoma medications. Failure was defined as a postoperative IOP ≥21 mm Hg with medications or loss of vision. Goldmann applanation tonometry was used for both pre- and postoperative IOP measurements. The postoperative IOP was recorded at all scheduled follow-up visits. The bleb failure mechanism was also described.

To determine the number of medications used, each topical medication was counted as 1 medication, while systemic carbonic anhydrase inhibitors were recorded as use and non-use.

Surgical Technique

Patients were anaesthetised with topical, subconjunctival, sub-Tenon, or general anaesthesia. A superior fornix-based conjunctival flap was performed. After careful homeostasis, a scleral flap in a trapezoid or rectangular fashion was created with a crescent blade at a depth of approximately two-thirds of the scleral thickness. Sponges soaked with MMC 0.2 mg/mL or 0.4 mg/mL were applied under the conjunctival and scleral flap for 2 to 4 minutes, followed by balanced salt solution (BSS) irrigation. Sclerostomy was performed using a 15° blade or puncher. Peripheral iridectomy was done and aqueous flow was checked. The scleral flap was repositioned with 2 to 3 interrupted or releasable sutures. The anterior chamber was formed with BSS. After conjunctival closure with 10-0 nylon or 8-0 vicryl sutures, leakage was checked. Subconjunctival or topical antibiotic and steroid were given at the end of surgery.

Postoperative medications consisted of a prednisolone acetate 1% eye drop every 2 hours, tapering over several weeks, in combination with an antibiotic eye drop 4 times daily. Antiglaucoma medication was added when the IOP was not satisfactorily controlled. The frequency of postoperative follow-up was planned on an individual basis, and was usually once a week for the first month.

Laser suture lysis was performed after surgery to titrate the IOP to the desired level, and included needling to regulate aqueous flow.

Statistical Analysis

Data were recorded using Microsoft Excel and analysed using the Statistical Package for the Social Sciences version 11.5. Chi-squared test and Fisher's exact test were used to evaluate categorical data. Continuous variables were analysed using unpaired Student *t* test. Mean IOP was analysed by analysis of variance. A p value of <0.05 was considered statistically significant.

Results

165 eyes of 141 patients treated with primary trabeculectomy with adjunctive MMC met the inclusion criteria. There were more

eyes in the MMC 0.4 mg/mL group (n = 129) than in the MMC 0.2 mg/mL group (n = 36) due to the longer period of use of this dose. The patients' baseline characteristics are summarised in Table 1. There was no difference between the groups except for preoperative lens status.

For the main outcome measure, no significant differences in late complications were found between the MMC 0.4 mg/mL and MMC 0.2 mg/mL groups. Similar to the late complications, there were no significant differences in early complications except for bleb leak at the limbus, which occurred more often in the MMC 0.2 mg/mL group (p = 0.007). The postoperative complications are shown in Table 2.

The mean preoperative IOP was 27.5 mm Hg (SD, 11.6 mm Hg) in the MMC 0.4 mg/mL group and 28.9 mm Hg (SD, 12.3 mm Hg) in the MMC 0.2 mg/mL group. Both groups achieved a mean decrease in IOP to a postoperative level of 13.7 mm Hg (SD, 5.0 mm Hg) in the MMC 0.4 mg/mL group and 14.9 mm Hg (SD, 5.6 mm Hg) in the MMC 0.2 mg/mL group after 2 years (Table 3). The mean IOP decrease was statistically significance for both groups (p < 0.05).

Table 1. Baseline characteristics of patients receiving mitomycin C 0.4 mg/mL or mitomycin C 0.2 mg/mL.

Characteristic	Number (%)	
	Mitomycin C 0.4 mg/mL (n = 129)	Mitomycin C 0.2 mg/mL (n = 36)
Sex		
Male	76 (59)	21 (58)
Female	53 (41)	15 (42)
Age (years)		
Mean (SD)	55.4 (13.6)	61.6 (8.9)
Range	22-81	26-82
Type of glaucoma		
Primary open angle	82 (64)	21 (58)
Primary angle closure	43 (33)	14 (39)
Unspecified primary glaucoma	4 (3)	1 (3)
Median number of topical antiglaucoma medications (interquatile range)	2 (2, 3)	3 (2, 3)
Use of systemic antiglaucoma medication	77 (60)	18 (50)
Baseline intraocular pressure (mm Hg)		
Mean (SD)	27.5 (11.6)	28.9 (12.3)
Range	10-69	8-60
Baseline visual acuity		
20/20-20/40	53 (41)	15 (42)
20/40-20/200	40 (31)	11 (30)
<20/200	36 (28)	10 (28)
Lens status		
Clear	40 (31)	5 (14)
Cataract	62 (48)	20 (56)
Others*	27 (21)	11 (30)

* Pseudophakia, aphakia, and no data.

Table 2. Early and late postoperative complications among patients receiving mitomycin C 0.4 mg/mL or mitomycin C 0.2 mg/mL.

Complication	Number (%)					
	Early			Late		
	Mitomycin C 0.4 mg/mL	Mitomycin C 0.2 mg/mL	p Value*	Mitomycin C 0.4 mg/mL	Mitomycin C 0.2 mg/mL	p Value*
Bleb leak						
Limbus	2 (1.6)	4 (11.1)	0.007	0 (0)	0 (0)	—
Bleb	2 (1.6)	0 (0)	0.452	0 (0)	0 (0)	—
Hypotony	37 (28.7)	15 (41.7)	0.138	24 (18.6)	3 (8.3)	0.141
Shallow/flat anterior chamber	14 (10.9)	2 (5.6)	0.660	3 (2.3)	1 (2.8)	0.139
Choroidal detachment	2 (1.6)	1 (2.8)	0.626	0 (0)	0 (0)	—
Blebitis	0 (0)	0 (0)	—	1 (0.8)	0 (0)	0.596
Bleb-related endophthalmitis	1 (0.8)	0 (0)	0.596	0 (0)	0 (0)	—
Hypotony maculopathy	1 (0.8)	0 (0)	0.596	0 (0)	0 (0)	—
Failed bleb						
Encapsulation	1 (0.8)	1 (2.8)	0.332	7 (5.4)	4 (11.1)	0.227
Episcleral bleb adhesion	0 (0)	0 (0)	—	1 (0.8)	1 (2.8)	0.332

* Chi-squared test.

Table 3. Mean intraocular pressures at baseline and follow-up among patients receiving mitomycin C 0.4 mg/mL or mitomycin C 0.2 mg/mL.

Time	Intraocular pressure (mm Hg) Mean (SD)	
	Mitomycin C 0.4 mg/mL (n = 129)	Mitomycin C 0.2 mg/mL (n = 36)
Baseline	27.5 (11.6)	28.9 (12.3)
Follow-up		
1 day	12.9 (8.4)	9.2 (5.7)
2 weeks	12.3 (6.7)	14.0 (9.0)
1 month	13.3 (7.5)	14.0 (6.5)
3 months	13.0 (5.9)	12.8 (5.9)
6 months	13.0 (6.2)	14.7 (7.7)
12 months	13.6 (6.6)	14.3 (4.5)
24 months	13.7 (5.0)	14.9 (5.6)
p Value	<0.001*	0.004*

* Analysis of variance.

The median number of topical antiglaucoma medications decreased from 2 preoperatively to 0 postoperatively for the MMC 0.4 mg/mL group, and from 3 preoperatively to 0 postoperatively for the MMC 0.2 mg/mL group. Only one patient in the MMC 0.4 mg/mL group received 1 systemic antiglaucoma medication postoperatively. The rate of postoperative cataract surgeries was greater in the MMC 0.4 mg/mL group than the MMC 0.2 mg/mL group. No significant differences were found between the groups for postoperative visual acuity and interventions (Table 4).

Two years after surgery, the complete success rate was significantly greater for the MMC 0.4 mg/mL group than for the MMC 0.2 mg/mL group ($p = 0.025_a$) [Figure 1]. There was a significantly higher failure rate in the MMC 0.2 mg/mL group ($p = 0.043_a$). However, there was no significant difference between the groups for qualified success ($p = 0.230_a$).

Discussion

MMC has been widely used in glaucoma surgeries. Although evidence suggests that MMC has a high impact on surgical success, it has the potential to cause serious complications. Chen et al performed a survey of MMC use among American and Japanese glaucoma specialists and found a wide range of concentrations used, from 0.01% to 0.08%, and exposure time, from 5 seconds to 7 minutes.[10] Analysis of the literature suggests that the success rate of MMC is not greatly affected by using a low concentration and short exposure time, but the complication rate rose considerably when these 2 variables were increased.[11-14] Jampel found that MMC 0.02% applied for 1 minute inhibited fibroblasts in vitro by 68%, which increased to 90% when MMC 0.04% was used for 5 minutes.[15] Currently, dosage and exposure time for MMC administration are adjusted individually according to the recommended guidelines and surgeons' experiences. This study was performed to determine the difference in late complication rates between 2 commonly used MMC concentrations at the authors' hospital.

In this study, there was no statistically significant difference in late complications between the 2 MMC concentrations overall, although the MMC 0.2 mg/mL group had a significantly higher rate of early bleb leak at the limbus. However, this could not be explained simply as the effect of MMC, as the surgical techniques could be implicated. Although hypotony, shallow or flat anterior chamber, choroidal detachment, blebitis, bleb-related endophthalmitis, and hypotony maculopathy occurred more frequently in the MMC 0.4 mg/mL group, there were no significant differences between the 2 groups at the 2-year follow-up.

The mean postoperative IOP resulted in a significant decrease for both groups. Comparison of the difference in mean IOP between groups at each follow-up visit was not done because the operations and MMC use were performed at different times. However, one study has shown that lower baseline IOP might offer a better chance of reaching the target IOP and achieving success after surgery.[6]

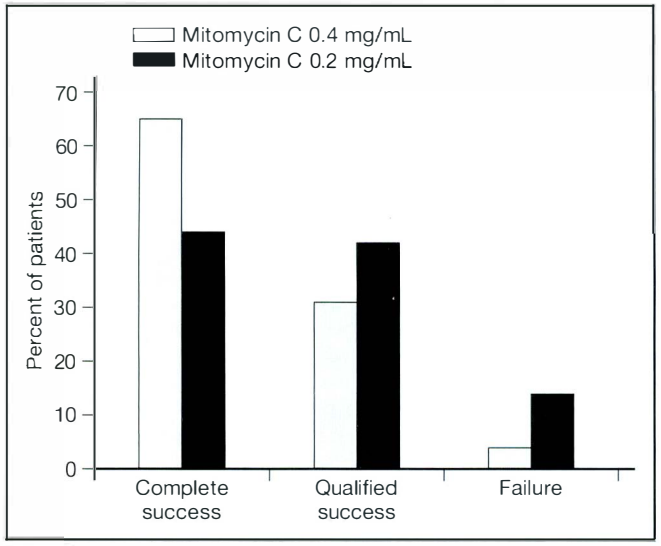
After 2 years, there were no differences in visual acuity, median number of antiglaucoma medications, and interventions

Table 4. Postoperative characteristics among patients receiving mitomycin C 0.4 mg/mL or mitomycin C 0.2 mg/mL.

Characteristic	Number (%)		p Value
	Mitomycin C 0.4 mg/mL (n = 129)	Mitomycin C 0.2 mg/mL (n = 36)	
Visual acuity			
20/20-20/40	34 (26)	12 (33)	
20/40-20/200	55 (43)	14 (39)	
<20/200	39 (30)	10 (28)	
No data	1 (1)	0 (0)	0.727*
Median number of topical antiglaucoma medications (interquatile range)	0 (0, 0)	0 (0, 1)	
Postoperative cataract surgery	24 (19)	2 (6)	0.057
Interventions			
Laser suture lysis	46 (36)	13 (36)	0.985*
Needling	11 (9)	3 (8)	0.971*

* Chi-squared test.

Figure 1. Success and failure rates of patients receiving mitomycin C 0.4 mg/mL or mitomycin C 0.2 mg/mL.



between the groups. Interestingly, the complete success rate was significantly higher for the MMC 0.4 mg/mL group and the failure rate was significantly higher for the MMC 0.2 mg/mL group. There was a significant difference in qualified success between the 2 groups.

Accelerated cataract progression is often seen after trabeculectomy. Studies have shown an association between trabeculectomy and lens opacity progression,[12,16-19] which results in increased postoperative cataract extraction. Noticeably, there was a higher rate of cataract surgery after trabeculectomy in the MMC 0.4 mg/mL group. It remains unclear whether adjunctive MMC directly contributes to cataract progression because few data have been reported. Similarly, this study did not show that a higher concentration of MMC was the cause of cataract progression because the preoperative lens status between the 2 groups was different. Many factors might be involved in the pathogenesis of cataract, including surgical technique and postoperative inflammation, interventions, and complications.

This study is limited by the difference in sample size, the study period, and inter-surgeon variability. Compared with other studies reporting on the incidence of complications of MMC, these results are different in some aspects, for example, hypotony and shallow anterior chamber. Comparison between studies depends on the definitions given in each report. However, the rates for serious complications such as hypotony maculopathy, choroidal detachment, blebitis, or bleb-related endophthalmitis are similar.[6,20-22] Blebitis and bleb-related endophthalmitis were low in this study, which may imply that both MMC 0.4 mg/mL and MMC 0.2 mg/mL can be acceptably used in terms of safety profile. However, MMC 0.4 mg/mL did have some advantages over MMC 0.2 mg/mL, with a higher complete success and lower failure rate after 2 years. Therefore, either concentration can be justifiably used clinically.

Although this study did not indicate which MMC concentration was optimal for Asian patients with primary glaucoma, it was clear that MMC 0.4 mg/mL was not more harmful than MMC 0.2 mg/mL. Although MMC 0.2 mg/mL was not as successful as MMC 0.4 mg/mL, the lower dose was effective for controlling IOP.

Late complications of MMC 0.4 mg/mL and MMC 0.2 mg/mL are not significantly different. The mean postoperative IOP decreased sufficiently with both doses. At 2 years postoperatively, MMC 0.4 mg/mL resulted in a higher complete success rate than did MMC 0.2 mg/mL. However, MMC 0.2 mg/mL was effective for postoperative IOP control. MMC 0.4 mg/mL was no more harmful than MMC 0.2 mg/mL.

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Efficacy of Cyclosporine A 0.05% Emulsion for the Treatment of Dysfunctional Tear Syndrome

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Aim: *To evaluate the efficacy of cyclosporine A 0.05% emulsion for the treatment of dysfunctional tear syndrome.*
Methods: *This randomised parallel prospective trial enrolled patients who had dysfunctional tear syndrome without lid margin with a severity level ≥2. Patients received unpreserved artificial tears in both eyes as needed and were randomised to receive adjunctive cyclosporine A 0.05% twice daily for 6 months in either the left or right eye. Patients were evaluated for signs and symptoms of dysfunctional tear syndrome at their first visit (baseline) and after receiving the study treatment at week 1 and months 1, 3, and 6.*
Results: *Twenty two of 26 enrolled patients completed the study. Most patients were women (73%), and the median age was 49 years (range, 31 to 73 years). Compared with baseline, both treatments significantly improved signs and symptoms of dysfunctional tear syndrome at almost all follow-up visits ($p < 0.05$). Compared with artificial tears, eyes treated with cyclosporine A had significantly greater increases in tear break-up time and greater improvements in Schirmer I test scores (without anaesthesia), rose bengal staining, conjunctival injection severity, and the Modified Ocular Surface Disease Index at months 3 and 6 ($p < 0.05$). Schirmer II test scores and fluorescein staining scores were significantly improved in cyclosporine A–treated eyes compared with artificial tears–treated eyes at month 3 ($p < 0.05$).*
Conclusion: *Concurrent treatment with cyclosporine A 0.05% emulsion and unpreserved artificial tears was effective for alleviating the signs and symptoms of dysfunctional tear syndrome.*

Key words: *Cyclosporine, Dysfunctional tear syndrome, Ophthalmic solutions*

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Introduction

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface.[1] Several validated survey instruments have documented that dry eye significantly affects the quality of patients' lives.[2,3] Approximately 10% to 20% of the western population is affected by dry eye.[4,5] A greater number of patients appear to have the disease in the Asia-Pacific region.[6,7] A recent study estimated that the prevalence of dry eye was 34% among adults older than 40 years in Thailand.[8]

The aetiology of dry eye is not known. Changes in the composition of tear film, including decreased mucin content, elevated osmolarity, and increased levels of inflammatory markers have been demonstrated to be associated with dry eye disease.[9-11] The term 'dysfunctional tear syndrome' (DTS) was proposed to reflect the role of abnormalities of tear film composition in the pathophysiology of dry eye, as not all patients have reduced tear volume.[12] Current evidence indicates that inflammation may play a major role in the development of DTS.[13,14] Lymphatic infiltration into the ocular tissues has been demonstrated in DTS, both in animal models and patients with Sjögren's or non-Sjögren's syndrome. The activation of T cells may result in the destruction of lacrimal glands or may disrupt the neuronal signals leaving the ocular surface, which in turn decreases the sensory input to the lacrimal glands and, as a corollary, reduces the quantity and quality of tears.[13,14]

Cyclosporine A (CsA) is an immunomodulator agent that binds to cyclophilin A and interrupts several signalling pathways in immune cells.[15] Topical administration of CsA 0.05% has been shown to decrease the number of activated T cells and expression of inflammatory markers in the conjunctiva of patients with DTS.[16,17]

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The aim of this study was to evaluate the efficacy of ophthalmic CsA 0.05% emulsion for the treatment of Thai adults with DTS.

Methods

This was a randomised parallel prospective clinical trial. The study was approved by the institutional review board, and all participating patients provided written consent before initiation of the study-specific procedures.

Patients

The main eligibility criteria were age 30 years or older, diagnosis of DTS without lid margin or altered tear distribution and clearance, and disease severity level ≥2 as defined by the Delphi panel of international experts.[12] Patients were diagnosed with DTS if both eyes had a Schirmer test value (without anaesthesia) of ≤10 mm/5 minutes, tear break-up time (TBUT) of ≤8 seconds, punctate corneal fluorescein staining score of ≥1 or filament keratopathy, conjunctival injection severity score of ≥1, and 1 or more DTS symptoms (tear film debris, discomfort, itching, photophobia, and red eye) of moderate severity (≥2). The primary exclusion criteria were uncontrolled severe systemic immune disease, active ocular infection or inflammatory disease, history of ocular surgery (eg, refractive surgery), or chronic eye disease (eg, glaucoma). Patients who wore contact lenses were also excluded from the study.

Study Design

All patients received unpreserved artificial tears (Cellufresh®; Allergan, Inc, Irvine, USA) in both eyes as needed and were randomised to receive adjunctive CsA 0.05% (Restasis®; Allergan, Inc) twice daily for 6 months in either the left or right eye. Patients were evaluated for signs and symptoms of DTS at the first study visit (baseline) and after starting the study treatments at week 1 and months 1, 3, and 6. Eyes treated with artificial tears alone served as control eyes to assess the efficacy of CsA 0.05%. The study was conducted in compliance with the regulations of the Health Insurance Portability and Accountability Act and the Declaration of Helsinki.

Efficacy Measures

At each study visit, patients were evaluated for signs and symptoms of DTS using Schirmer I and II tests, TBUT, ocular surface staining (fluorescein and rose bengal), conjunctival injection severity, and the Modified Ocular Surface Disease Index (MOSDI). Changes in the signs and symptoms of DTS from baseline were used to assess the efficacy of the study treatments.

Schirmer I test was performed without anaesthesia. Schirmer II test was carried out by irritating the nasal mucosa after topical administration of 0.5% proparacaine hydrochloride anaesthetic. The TBUT was measured using a sterile fluorescein paper diluted with a non-preserved balanced salt solution. Corneal fluorescein staining was evaluated by slit lamp using a yellow filter and cobalt blue illumination; the staining was graded as: 0 = none; 1 = mild; 2 = moderate; and 3 = severe. Ocular surface staining with rose bengal was graded using the van Bijsterveld scoring system (a 3-point scale ranging from 0 to 9). Conjunctival injection was examined by slit lamp and was graded using a scale of 0 = none; 1 = mild, non-specific conjunctivitis; 2 = moderate conjunctivitis ± chemosis; and 3 = severe conjunctivitis.

The OSDI was modified by including additional questions for tear film debris, discomfort, itching, photophobia, and red eye. MOSDI questions were rated from 0 = none of the time to 4 = all of the time. A negative change from baseline indicated an improvement.

Statistical Analysis

The results were presented as mean (SEM). Paired Student *t* test (2-sided) was used to analyse intra-group changes from baseline in continuous variables. Inter-group comparisons were performed using the paired Student *t* test. A p value of <0.05 was considered statistically significant. Analyses were conducted using the Statistical Package for the Social Sciences version 11.0.

Results

Patients' Demographics

Twenty six patients enrolled in the study from 1 September 2005 to 1 July 2007. Most patients were women (73%), and the median age was 49 years (range, 31 to 73 years) [Table 1]. Four patients did not complete the study; 3 patients were lost to follow-up, and 1 patient discontinued the study because of a burning sensation in the conjunctiva and cornea (Table 1). Of the 26 patients included in the analyses, 23 patients had a disease severity of level 2, and 3 patients had a disease severity of level 3 at study entry.

Table 1. Patients' characteristics (n = 26).

Characteristic	Number of patients (%)
Sex	
Female	19 (73)
Male	7 (27)
Age (years)	
Median (range)	49 (31-73)
Number of patients at each follow-up visit	
Day 7	26 (100)
Month 1	26 (100)
Month 3	23 (88)
Month 6	22 (85)
Reason for discontinuation	
Lost to follow-up	3 (11)
Adverse events	1 (4)

Change in Outcome Measures from Baseline

Compared with baseline, both study treatments significantly increased Schirmer I test scores and TBUT, and significantly decreased fluorescein and rose bengal staining, conjunctival injection severity, and MOSDI scores at all follow-up visits ($p < 0.05$). Schirmer II test scores were significantly improved at months 1 and 3 compared with baseline for both treatments ($p < 0.05$). At month 6, the mean Schirmer II test score increased from baseline by 6.68 mm in eyes treated with artificial tears and 8.45 mm in eyes treated with CsA ($p < 0.002$).

Intergroup Comparison of Outcome Measures

The increases in Schirmer I test scores were similar in both treatment groups at day 7 and month 1 (Figure 1). The mean Schirmer I test score increased at months 3 and 6 by 2.35 mm and 3.50 mm, respectively, in eyes receiving artificial tears and by 3.65 mm and 5.64 mm, respectively, in eyes treated with CsA. The increases in tear production from baseline were significantly greater for eyes treated with CsA than for those treated with artificial tears alone at both month 3 ($p = 0.035$) and month 6 ($p = 0.02$) [Figure 1].

The increases in Schirmer II test scores from baseline were numerically higher for eyes treated with CsA than for those treated with artificial tears alone at all follow-up visits. The difference between the study treatments reached a statistically significant level ($p = 0.002$) only at month 3, when the mean increase in tear production from baseline was 7.13 mm in the CsA-treated eyes and 3.56 mm in the eyes receiving artificial tears alone. The difference between the groups was not statistically significant at month 6.

Figure 1. Changes in mean Schirmer I test scores (without anaesthesia) from baseline.
* $p = 0.035$.
† $p = 0.020$.

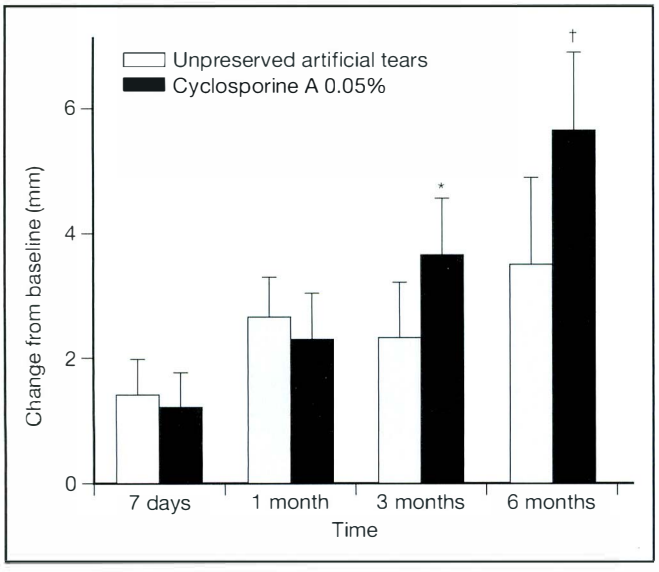
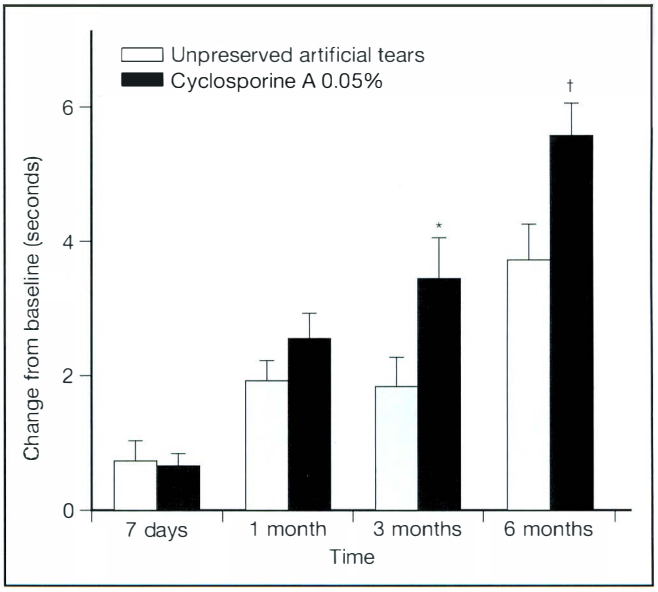


Figure 2. Changes in mean tear break-up time from baseline.
* $p = 0.002$.
† $p = 0.001$.



The mean TBUT in the eyes receiving artificial tears alone increased from baseline by 1.83 seconds and 3.73 seconds at months 3 and 6, respectively (Figure 2). The increases in TBUT were significantly greater for the eyes treated with CsA than for those treated with artificial tears alone at both month 3 (3.43 seconds; $p = 0.002$) and month 6 (5.59 seconds; $p = 0.001$).

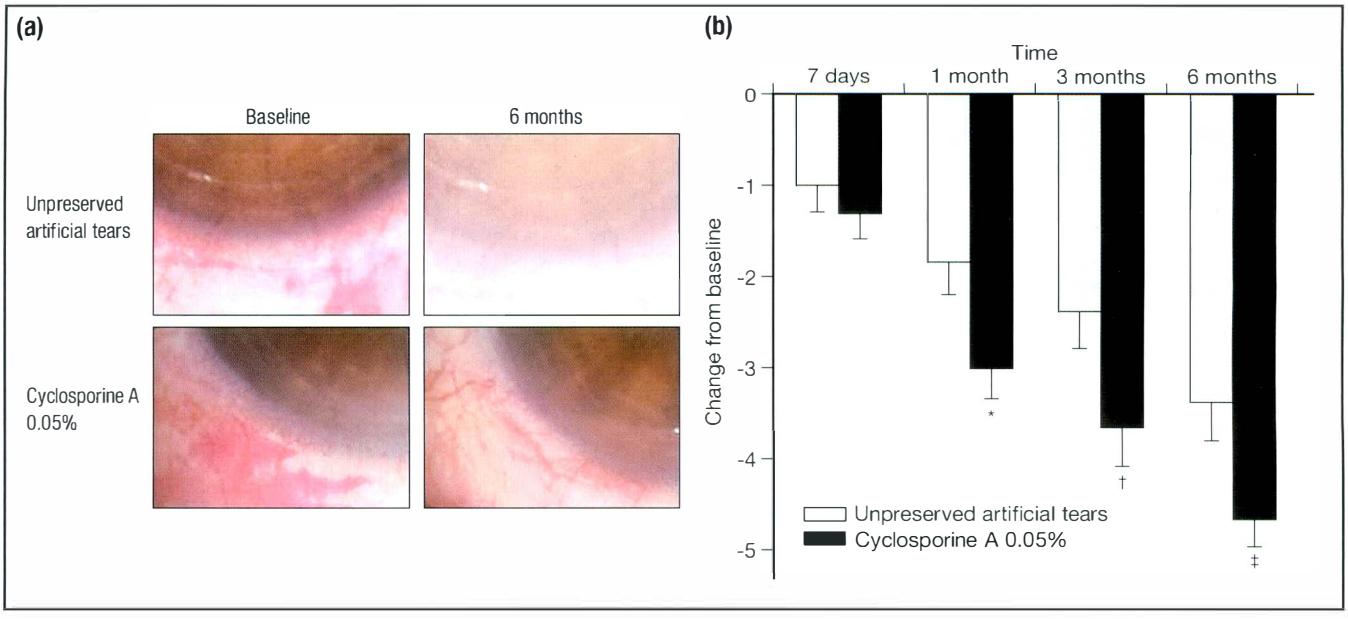
The decreases in corneal fluorescein staining scores from baseline were numerically greater in eyes treated with CsA than those treated with artificial tears alone at all follow-up visits. The difference between the study treatments was statistically significant ($p = 0.038$) at month 3, when the mean decrease in fluorescein staining from baseline was -0.96 in eyes treated with CsA and -0.48 in eyes treated with artificial tears.

Representative images of ocular staining with rose bengal at baseline and month 6 are presented in Figure 3a. The mean rose bengal staining scores of eyes receiving artificial tears alone decreased from baseline by -1.85, -2.39, and -3.36 at months 1, 3, and 6, respectively. CsA decreased rose bengal staining scores from baseline significantly more than artificial tears alone ($p = 0.01$) [Figure 3b].

The decrease in conjunctival injection severity scores from baseline was significantly greater for eyes receiving artificial tears (-0.61) than CsA-treated eyes (-0.38) at day 7 ($p = 0.031$). At months 3 and 6, the decreases in conjunctival injection severity scores were significantly greater in eyes treated with CsA than in those treated with artificial tears alone ($p = 0.022$ and $p = 0.042$, respectively) [Figure 4]. The mean decrease from baseline in conjunctival injection severity scores at months 3 and 6 were -1.30

Figure 3. Ocular staining with rose bengal. (a) Representative images of eyes treated with artificial tears alone or in combination with cyclosporine A 0.05% at baseline and month 6; and (b) changes in mean rose bengal staining scores from baseline.

* p = 0.009.
† p = 0.004.
‡ p = 0.005.



and -1.59, respectively, in eyes receiving artificial tears and -1.52 and -1.77, respectively, in eyes treated with CsA.

The mean decrease in MOSDI scores from baseline was similar for both groups at day 7 and month 1. However, MOSDI scores decreased significantly more in eyes treated with CsA at months 3 and 6 (-6.91 and -8.09, respectively) compared with eyes treated with artificial tears alone (-5.48 and -6.14, respectively) [Figure 5].

Adverse Events

One patient (4%) receiving CsA experienced a burning sensation and discontinued the study at month 3 (Table 1). No other adverse events were reported during the study.

Figure 4. Changes in mean conjunctival injection severity scores from baseline.

* p = 0.031.
† p = 0.022.
‡ p = 0.042.

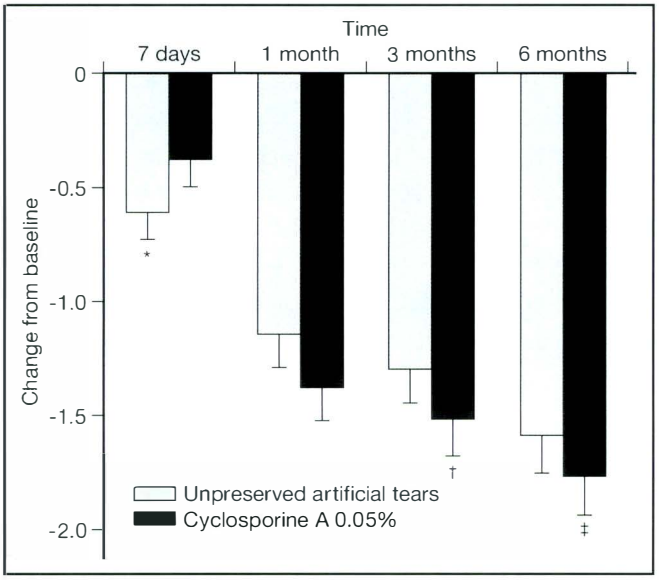
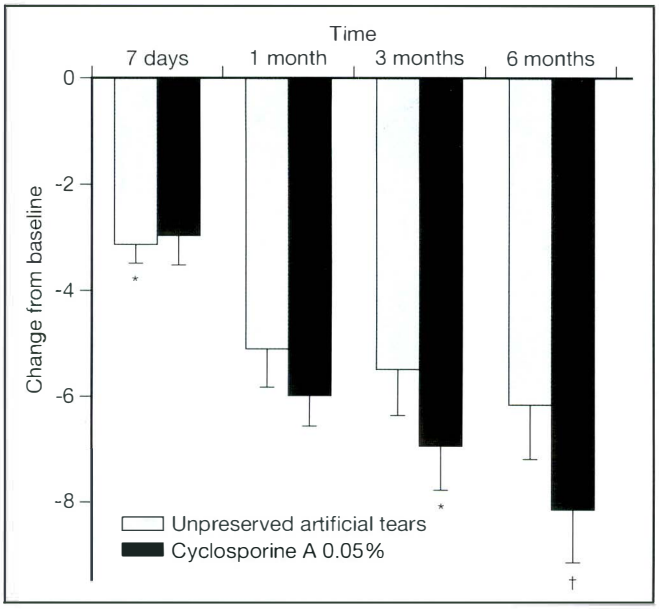


Figure 5. Changes in mean Modified Ocular Surface Disease Index scores from baseline.

* p = 0.023.
† p = 0.002.



Discussion

This study demonstrated that concurrent treatment with CsA and artificial tears was more efficacious than treatment with artificial tears alone for alleviating the signs and symptoms of DTS. Topical CsA was well tolerated with no reports of serious adverse events. These findings suggest that CsA is safe and effective for the treatment of patients with DTS with a disease severity level ≥2 without lid margin disease as defined by the Delphi panel of international experts.[12]

Treatment of DTS is challenging as the correlation between the signs and symptoms is weak, and the efficacy criteria are often not uniform among studies.[1,8] Therefore, a combination of different clinical tests is commonly used to assess the efficacy of a treatment for DTS. In this study, CsA significantly reduced the signs of DTS from baseline and resulted in greater improvements than in eyes treated with artificial tears alone in all tests. Consistent with previous studies,[19,20] the improvements in the clinical signs for CsA generally reached statistically significant levels by month 3 and continued to be significantly greater than the improvements in eyes treated with artificial tears at month 6. These findings suggest that patients' education and adherence to the therapy are necessary to successfully manage DTS.

The Delphi panel of international experts has recently recommended that patients' symptoms should be given primary consideration when determining disease severity.[12] The OSDI is a valid and reliable instrument for assessing the severity of DTS symptoms and their effects on vision-related functions.[3] The MOSDI used in this study included 5 additional questions to the OSDI questionnaire. Topical treatment with CsA alleviated the severity of patients' symptoms significantly more than treatment with artificial tears alone at months 3 and 6. Hence, a good correlation between subjective and objective outcomes was observed in this study.

Several studies have been conducted in the USA to assess the efficacy and safety of CsA for the treatment of DTS. Topical administration of CsA for up to 3 years was found to be safe, with no reports of serious adverse events.[20] Similar to the findings of this study, other studies have demonstrated that CsA significantly increased tear production and decreased the intensity of ocular staining and severity of symptoms for patients with moderate-to-severe DTS.[19,21] Topical CsA therapy also decreased the dependency on artificial tears of patients with DTS.[19,22]

The prevalence of DTS appears to be approximately 2 to 3 times higher in the Asia-Pacific population than in Caucasian people.[4-7] Therefore, effective management strategies are needed to alleviate symptoms of DTS and improve patients' quality of life. The findings of this study confirmed the results of previous trials and demonstrated that CsA significantly alleviated the signs and symptoms of DTS for Thai adults, with a disease severity level ≥2 who did not have lid margin disease. Large clinical trials are warranted to assess the effect of CsA therapy on patients' quality of life.

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Treatment and Prevention of Ocular Bacterial Infections in Asia Part I: the Changing Landscape of Microbial Organisms

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Asia faces unique challenges in the treatment of ocular infections. Aside from regional differences in the epidemiology of disease and bacterial resistance, culture and tradition colour the landscape, playing an important role in approaches to health care delivery. Part I of this 2-part series describes current local and regional trends for ocular infections and microbial resistance in Asia, and how these factors shape the need for modern solutions to improve patient outcomes. Part II will examine the limitations of older antibiotics, the evolution of the newly developing fluoroquinolones, and the role of the fourth-generation fluoroquinolone, moxifloxacin.

Key words: *Anti-bacterial agents, Asia, Drug resistance, bacterial, Epidemiology, Eye infections, Fluoroquinolones*

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Cultural and Regional Approaches to Treatment

Regional trends in socioeconomic development underlie much of Asia's changing landscape. Many Asian people still reside and work in the relative isolation of rural areas, where delays in reaching needed medical care and supplies have a profound impact on health and the quality of life. Grassroots local health workers are often the only people available to deliver immediate treatment. These individuals have been shown to greatly impact the prevention of post-traumatic corneal ulceration after corneal abrasion, for example, in isolated rural villages of Bhutan, but only if equipped with appropriate antimicrobial agents.[1]

A frequent source of ocular infection in these regions is trauma. A 2-year survey in the Kathmandu Valley region of Nepal described the almost epidemic incidence of 4% ocular trauma and 2% corneal abrasion and ulcers in the population. When antibiotic prophylaxis was initiated within 18 hours of injury, no patients progressed to a corneal ulcer. However, 3.9% of patients who presented 18 to 24 hours after injury, and 28.6% who those presented 24 to 48 hours, after injury subsequently progressed to corneal ulceration. This study showed a high prevention rate for post-traumatic corneal ulceration in this rural setting when antibiotic treatment (in this case, chloramphenicol ointment) was initiated in a timely fashion.[2] Changing trends in China over a 30-year period showed that, from the 1970s, ordinary trauma outweighed occupational trauma as a cause of corneal blindness, and rural and urban areas were equally represented. Avoiding infection after foreign body injury to the cornea was reportedly a primary concern.[3]

Predominantly rural areas may also be inclined to use traditional eye medicines (TEM) for the treatment of corneal ulcers, particularly after trauma. In one area of South India, 47.7% of patients presenting with a corneal ulcer had used TEM, with no differentiation for age and sex. These treatments included human breast milk, leafy matter, castor oil, and hen's blood, a circumstance that underscores the need for better education of the population and access to appropriate medical treatments. These local customs persisted despite a population otherwise educated about modern advances, such as cataract surgery and intraocular lens implantation.[4]

Regional Epidemiology of Ocular Infections

Bacterial Keratitis

The profile of microorganisms causing bacterial keratitis may vary regionally, making data describing local trends in bacterial susceptibility useful for the selection of appropriate topical antibiotics. While the proportion of selected pathogens may vary

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with region, the data indicate that effective antimicrobial agents, along with easier availability and access to medical care are needed.

In The Philippines, a 30-year survey (from 1971 to 2001) by Valenton,[5,6] studied the various causes of central microbial keratitis in 4170 patients. In this survey, bacteria accounted for 52% of infections (n = 2178), followed by viruses for 22% (n = 915), fungi for 13% (n = 540), and finally amoeba for only 0.2% (n = 8). The remaining infections (n = 529) were of undetermined aetiology. Of the documented bacterial aetiologies, *Moraxella* spp (29%), *Pseudomonas* spp (28%), and *Staphylococcus* spp (25%) comprised the majority of causative organisms. In this population of patients, trauma (76.6%) was the leading predisposing factor.

In Taiwan, a 12-year study (from 1994 to 2005) examined in vitro antibiotic susceptibility trends from bacterial keratitis isolates.[7] Of the 272 identified pathogens, *Pseudomonas* spp were identified most often (46.7%), followed by *Staphylococcus* spp (11.0%), *Propionibacterium* spp (8.1%), *Streptococcus* spp (7.6%), and non-tuberculous mycobacteria (6.6%). During this period, no significant changes occurred in microbial sensitivities for *Staphylococcus* spp, *Streptococcus* spp, *Pseudomonas* spp, or non-tuberculous mycobacteria, with 95.8% of gram-negative organisms remaining susceptible to the fluoroquinolone, ciprofloxacin.[7] A study from Singapore (from 1992 to 1993) also found that bacterial keratitis was most commonly due to gram-negative bacteria (80.4%) with *Pseudomonas aeruginosa* the most frequent organism overall, and the most frequent in contact lens ulcers (78.6%).[8]

However, in Japan, during the 5-year period from 1999 to 2003, among 99 different organisms isolated from bacterial keratitis samples, the majority (77.8%) were gram-positive bacteria, with only 18.2% being gram-negative bacteria (and 1 case of *Acanthamoeba* spp).[9] The primary risk factor for microbial keratitis in this study was contact lens wear, present in 54.5% of cases. In contrast, a study from South India showed that when microbial keratitis was associated with contact lens wear, *Pseudomonas* spp were the most commonly isolated organisms (52%).[10]

In rural Bangladesh, *Streptococcus pneumoniae* and *Pseudomonas* spp were described as the most common causes of microbial keratitis, overall,[11] but tropical developing countries, such as India and Ghana, report that fungi cause most cases. *Pseudomonas* spp were the most frequently isolated bacteria from suppurative corneal ulcers in Ghana, but streptococci were the most common in India, emphasising that knowledge of local aetiological factors is essential for the management of infectious keratitis.[12] Interestingly, a fundamentally different profile was found in a worldwide survey of infectious keratitis after LASIK, where atypical mycobacteria and staphylococci were most frequently implicated.[13]

Acanthamoeba Keratitis

Keratitis due to *Acanthamoeba* spp occurs infrequently, but may have a shifting prevalence in rural areas. In Valenton's 30-year survey of *Cornea and External Eye Disease Problems in The Philippines*, *Acanthamoeba* spp was identified in only 8 of 4170 eyes (0.2%) with central keratitis.[5] In South India, *Acanthamoeba* keratitis accounted for 1.04% of corneal ulcers from rural areas during a 3-year period, with most (72.7%) occurring in patients younger than 51 years. Agricultural workers accounted for 78.79% of patients, and all patients had a history of corneal injury, 84.85% due to mud. TEMs had been used by approximately one-third of these patients. Delayed diagnosis and inappropriate antimicrobial therapy were identified as primary risk factors for a poor visual outcome.[14]

Conjunctivitis

The micro-organisms commonly causing acute bacterial conjunctivitis in adults in the USA include *Staphylococcus aureus*, *S pneumoniae*, gram-positive anaerobes (*Peptostreptococcus* spp) *Haemophilus* spp (*H influenzae* and *H influenzae* biogroup *aegyptius*), and *Streptococcus pyogenes*, with *H influenzae*, *S pneumoniae* and *Moraxella catarrhalis* being most common in children. Chronic conjunctivitis may be caused by *Moraxella lacunata*, *Klebsiella pneumoniae*, *Serratia marcescens*, and *Escherichia coli*.[15] In The Philippines, Valenton's study also showed that among bacterial conjunctivitis, *Staphylococcus* spp was the primary cause, with an incidence of 44.2%.[5,6] This was followed by *Moraxella* spp (22.6%), *Neisseria gonorrhoeae* (18.5%), and *Haemophilus* spp (12.2%). *S pneumoniae*, on the other hand, accounted for only 1.3% of cases.

The treatment of conjunctivitis in developing regions worldwide may be complicated by profound differences in the availability of medical care, socioeconomic factors, and culture. An epidemic outbreak of acute haemorrhagic conjunctivitis in rural communities is likely to have profound economic consequences.[16] In one study, positive cultures for superinfection were found in 86% of patients with corneal ulceration, with *P aeruginosa* found in 25% and *S aureus* in 16% (with *Fusarium* spp and *Aspergillus* spp in 25% and 16%, respectively).[17] Conjunctivitis was the most common ocular infection among primary school children and was similar in type and prevalence in both rural and urban slum areas of Delhi. There was a rise in incidence with increasing age and a significant association between ocular infections and religion, but not per capita income.[18]

Other Ocular Infections

In developing countries, penetrating injuries pose a particular hazard because immediate medical treatment is often inaccessible.

In a study of microbial cultures in open globe injuries in southern India, corneoscleral laceration and delay in surgical intervention were among the factors contributing to a positive microbial culture.[19]

Other ocular infections also show regional differences. In one region, the causative organisms of chronic dacryocystitis and dacryoabcess showed a shift to a higher incidence of gram-negative organisms (61%) versus gram-positive organisms (39%), with *Pseudomonas* spp being the most common organism (22%) followed by *S aureus* (13%), *Enterobacter* (10%), *Citrobacter* (10%), *S pneumoniae*, *E coli*, and *Enterococcus* spp (7%). Some uncommon gram-negative organisms were also isolated, including *Alcaligenes* spp (5%) and *Stenotrophomonas maltophilia* (2.5%). Less than 30% of gram-negative isolates were sensitive to cefalexin and ampicillin.[20] In an Indian hospital, some cases of ophthalmia neonatorum were found to be culture-positive for bacterial species, *P aeruginosa* being the most common, with the highest sensitivity to the fluoroquinolone antibiotics.[21]

Endophthalmitis

Even in the best of circumstances, treatment of infectious endophthalmitis is considered a medical emergency, with early intervention key to an optimal visual outcome. In remote regions of the world, this may not be possible, and prevention becomes more important. In a study of post-traumatic endophthalmitis in South Vietnam, the mean time interval from trauma to diagnosis was 16.8 days (SD, 5.6 days) and visual acuity at the time of diagnosis was finger counting only or light perception in 96% of patients.[22] Positive cultures showed 51% gram-positive bacteria and 33% gram-negative bacteria (and 16% fungi). Noted among significant risk factors for a poor prognosis were a purely corneal wound, surgical intervention more than 24 hours after the trauma, a rural setting, and inadequate antibiotic treatment. The authors stressed the importance of comprehensive antibiotic treatment at the time of injury to the eye.[22]

Prevention of postoperative endophthalmitis after cataract surgery relies heavily on pre- and perioperative administration of local antibiotics and cleansing of the surface of the eye. Here again, availability of broad-spectrum effective antibiotics is a critical part of modern prophylactic regimens. The importance of topical antibiotic delivery is also underscored by reports that describe a higher incidence of postoperative endophthalmitis in patients not receiving a subconjunctival injection of antibiotic.[23,24] Although this route of prophylaxis has lost favour in recent years, such reports support the usefulness of local antibiotic delivery during surgery to help reduce the ocular surface flora and incidence of endophthalmitis.[23,24] In recent years, the intracameral route of injection has also been used by some clinicians for prophylaxis of post-cataract surgical infection.[25-29]

Data from the USA[30] and Asia[31] identify gram-positive organisms as the primary causes of culture-proven postoperative endophthalmitis, led by *Staphylococcus epidermidis* (coagulase-negative staphylococci) and *S aureus*. However, as endophthalmitis may also be caused by gram-negative species and virulent strains that result in poor visual outcomes, broad-spectrum treatment, and prophylaxis, are appropriate. Some data suggest that the rates of postoperative endophthalmitis in Asia are similar to rates reported worldwide.[31] However, regional differences play a role if one considers that contamination during surgery often occurs from the patient's own flora. Differences between ethnic groups in Asia, such as pre-existing diseases, anterior chamber contamination, and anterior blepharitis have been cited as regional risk factors.[31]

Regional Shifts in Susceptibility of Ocular Isolates

Data describing a gradual increase in bacterial resistance of ocular isolates have been accumulating over the years, but are more difficult to obtain than data describing more generalised infections. These changing bacterial resistance patterns, documented by local bacterial susceptibility and epidemiological data, where available, help to guide the selection of appropriate topical antibiotic therapy. Table 1 presents local bacterial susceptibility data from Manila Doctors Hospital and The Medical City, both premier tertiary care facilities in Manila, The Philippines, that support these worldwide trends, showing substantially diminished susceptibility of important bacteria to commonly used antibiotics.

In Beijing, China, 347 ocular isolates were tested during the 2-year period from 1999 to 2000.[32] Gram-positive cocci accounted for 55.3% of isolates, gram-negative cocci for 4.6%, gram-positive bacilli for 12.7%, gram-negative bacilli for 25.7%, and *Nocardia* spp for 1.7%. Overall resistance rates of 26% to 35% to the earlier fluoroquinolones, ofloxacin, ciprofloxacin, and norfloxacin, were detected. *Streptococcus* spp showed 52.9% and 70.6% resistance to gentamycin and tobramycin, respectively, and 23.5% to norfloxacin, but resistance was lower to ofloxacin (5.9%) and ciprofloxacin (11.8%). *Pseudomonas* spp were significantly more resistant (42%) to gentamycin than to the fluoroquinolones (6% to 14%). *Staphylococcus* spp were equally susceptible to gentamycin/tobramycin and ofloxacin/ciprofloxacin. The fluoroquinolones, ofloxacin and ciprofloxacin, had better overall in vitro activity during those years.

In India, significant resistance of *S aureus* isolates from patients with keratitis was already noted in one study performed from 1993 to 2000, in which 20.6% of isolates showed resistance to ciprofloxacin.[33] In a 6-year period, from 1991 to 1997, 30.7% of 1558 corneal isolates from culture-proven bacterial keratitis had become resistant to ciprofloxacin.[34] This included 32.5% of the

Table 1. Surveillance of antibiotic resistance patterns of bacterial isolates from January to December 2007 at Manila Doctors Hospital and The Medical City, Manila, The Philippines.

Antibiotic	Bacterial isolates (% sensitive)		
	*Staphylococcus aureus**	*Streptococcus epidermidis*	*Pseudomonas aeruginosa*
Amikacin			—/92.0
Ceftazidime			—/97.3
Cefuroxime sodium			0/—
Chloramphenicol	52.4/—†	69.7/—	
Ciprofloxacin	50.8/89.0	38.1/82.0	75.7/96.0
Erythromycin	44.1/66.5	22.8/62.3	
Gatifloxacin		56.2/—	
Gentamycin	66.9/—	53.1/—	71.4/81.0
Levofloxacin	85.5/66.5	57.8/85.7	45.5/—
Linezolid	—/100.0	—/100.0	
Moxifloxacin		50.0/—	
Norfloxacin	67.4/—	50.0/—	
Ofloxacin	28.6/—	43.4/—	—/71.5
Oxacillin	—/89.5	—/69.7	
Tetracycline	56.7/—	40.8/—	
Tobramycin		40.0/—	78.1/—
Vancomycin	93.0/100.0	95.4/100.0	

* Of 113 specimens of metnicillin-resistant *Staphylococcus aureus* identified, only 1 isolate was ocular.
† Data from Manila Doctors Hospital/data from The Medical City.

gram-positive cocci, 10.0% of the gram-positive bacilli, 13.3% of the gram-negative organisms, and 35.1% of the *Actinomycetes* and related organisms.

In South Australia, resistance to cephazolin, the current first-line antibiotic for gram-positive cocci during the study period 1998 to 2003, was noted in 35% of cases due to coagulase-negative *Staphylococcus*.[35] However, all *Pseudomonas* isolates remained susceptible to ciprofloxacin. In the USA, resistance to the early fluoroquinolones was detected somewhat later than in Asia.[36] Resistance to ciprofloxacin in corneal and conjunctival isolates of *S aureus* rose from a mean 8.0% during 1990 to 1995 to 20.7% during 1996 to 2001. In South Florida, in vitro resistance of *S aureus* isolates to ofloxacin and ciprofloxacin increased from 11% in 1990 to 28% in 1998, showing a 3-fold increase.[37] In a slightly different region, *S aureus* resistance to ciprofloxacin and ofloxacin increased yearly from approximately 5% to 35% between 1993 and 1997, and significant resistance of *Streptococcus* spp and coagulase-negative *Staphylococcus* spp was noted, remaining unchanged during this period.[38] However, gram-negative organisms remained susceptible to fluoroquinolones throughout.

These basic trends underlie the need to examine more closely newer antibiotics such as the fluoroquinolones. In Part II of this series, the characteristics and applicability of these agents, and moxifloxacin in particular, for the prevention and treatment of ocular infections will be examined.

Conclusions

Changes in worldwide bacterial resistance patterns and the epidemiology of ocular infections throughout Asia pose unique challenges for the management of ocular infections in these regions, both rural and urban. Access to effective and safe broad-spectrum topical antibiotics are paramount to addressing these needs. Better access by local health workers to effective and safe topical antibiotics is cited as a primary factor for improving patient outcomes and quality of life.

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Treatment and Prevention of Ocular Bacterial Infections in Asia Part II: the Changing Landscape of Antibiotic Treatment

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Asia faces unique challenges in the treatment of ocular infections. Aside from regional differences in the epidemiology of disease and bacterial resistance, culture and tradition colour the landscape, playing an important role in approaches to health care delivery. In the first of a 2-part series, current local and regional trends in ocular infections and microbial resistance in Asia, and how these factors shape the need for modern solutions to improve patient outcomes were described. In this Part II, the limitations of older antibiotics, the evolution of the newly developing fluoroquinolones, and the role of moxifloxacin, a fourth-generation fluoroquinolone, are examined.

Key words: *Anti-bacterial agents, Asia, Drug resistance, bacterial, Eye infections, Fluoroquinolones, Therapeutics*

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Shifting Regional Microbial Resistance

Important changes in antimicrobial resistance to traditionally used antibiotics have emerged over the years, so that interest is increasingly focused on the newly developed antibiotics. Methicillin-resistant *Staphylococcus aureus* and *Streptococcus pneumoniae*, both less susceptible to the β-lactam and macrolide antibiotics, are spreading worldwide. *Enterococcus* spp and many gram-negative species show increased resistance to vital anti-biotics such as vancomycin and the β-lactams, and microbes such as *Chlamydia* spp and *Mycoplasma* spp have emerged as important clinical pathogens. A steady increase in β-lactamase production among *Haemophilus influenzae* isolates has been documented since 1973, already estimated at 20% by 1986. Resistance to chloramphenicol and tetracycline was frequently reported through-out Europe and Asia with multiple antimicrobial resistance mechan-isms described in those regions as well as in the USA.[1]

Increasing resistance among the respiratory pathogens, in particular *S pneumoniae*, *H influenzae,* and *Moraxella catarrhalis*, is occurring at an alarming rate worldwide.[2] Penicillin resistance of *S pneumoniae* isolates reportedly varies by geographical location, with rates exceeding 20% in the USA, Mexico, Japan, Saudi Arabia, Israel, Spain, France, Greece, Hungary, and the Slovak Republic, and exceeding 50% in South Africa, Hong Kong, Taiwan, and South Korea. Diminished susceptibility to penicillin is associated with macrolide resistance, which has a prevalence rate of 70% to 80% in some Asian countries. Resistance to trimethoprim-sulfamethoxazole and tetracycline are also associated with this multiple resistance. However, despite the fact that β-lactamase production has increased among some respiratory pathogens, the 'respiratory' fluoroquinolones have remained active against a majority of these pathogens, including atypical mycobacteria.[3,4] *Mycoplasma* spp and *Chlamydia* spp play an increasingly important role in respiratory tract infections. These microorganisms are not susceptible to β-lactams as *Chlamydia* spp are obligate intracellular pathogens and *Mycoplasma* spp do not exhibit the typical rigid bacterial cell wall. While the early quinolone antibiotics had poor activity against these atypical microbes, the newer classes of fluoroquinolones, including moxifloxacin, exhibit high activity against these species.[5]

These fundamental changes in bacterial susceptibility around the world and in Asia have been linked to factors such as bacterial mutations, resistance in nosocomial infections,[6] overuse or misuse of antibiotics,[7] antibiotic use in animals, agriculture, and fisheries, introduction of foreign work forces or expatriate populations, and easy availability of antibiotics without prescription, particularly in developing countries as in the Gulf region,[8-10] India,[11-13] Korea,[14-16] Thailand and South East Asia,[17] Malaysia,[18] and Japan.[19] The use of

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antibiotics in animals has also contributed to bacterial resistance, although a recent study in Asia showed that resistance by selected pathogens to the fluoroquinolones has not yet been observed.[20]

Part I of this article presented local bacterial susceptibility data from Manila Doctors Hospital and The Medical City, both premier tertiary care facilities in Manila, The Philippines, that support these worldwide trends, showing substantially diminished susceptibility of important bacteria to commonly used antibiotics. However, today, modern fluoroquinolones have evolved with targeted modifications that deliver effective antibiotic activity against a host of important pathogens.

History of Fluoroquinolone Development

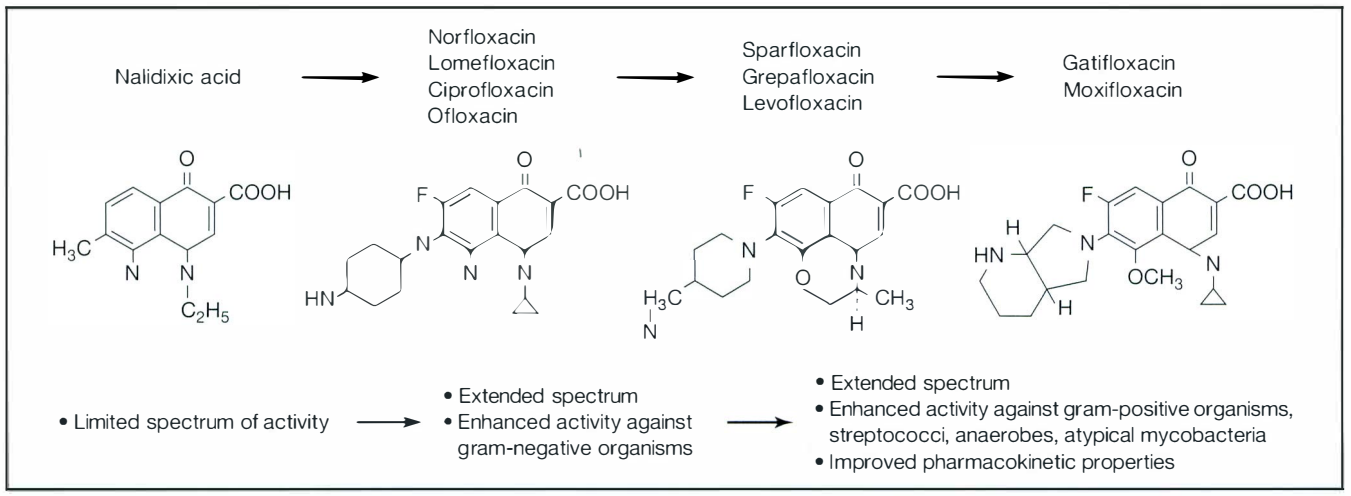
Modern fluoroquinolone antibiotics originated from work with chloroquine, an antimalarial agent modified to a compound showing antibacterial activity. Nalidixic acid (NegGram) was the first fluoroquinolone antibiotic, patented in 1962. Nalidixic acid had a limited spectrum of action, only against some gram-negative bacteria and, being poorly absorbed orally, was useful primarily for the treatment of urinary tract infections.

Through extensive research in ensuing years, the nalidixic acid molecule was modified to produce more useful compounds by adding stepwise improvements that expanded the antimicrobial activity and added features (Figure 1). Introduction of a piperazinyl side chain at position 7 improved activity against gram-negative bacteria and the piperazine ring enhanced bacterial cell wall penetration as well. Fluorination at position 6, patented in 1973, created better activity against gram-positive bacteria. The combination of these 2 modifications produced norfloxacin, the first 6-fluorinated compound, patented in 1978. Subsequent research moved rapidly, leading to the development of ciprofloxacin, a compound with an added cyclopropyl side chain at position 1, patented in 1981, and to ofloxacin in 1982. Ofloxacin and its l-isomer, levofloxacin, added a bridging ring between the N-1 and position 8, extending efficacy against gram-positive microbes, including *S pneumoniae*, while maintaining the characteristically good activity against gram-negative species of the earlier fluoroquinolones. These antibiotics were well absorbed from the gastrointestinal tract, facilitating their use for the treatment of systemic infections.

Modifications that created moxifloxacin incorporated a cyclopropyl group side chain at the position 1 nitrogen, which imparted better activity against gram-negative microbes, and substitutions such as the diazabicyclic ring at position 7 also made it relatively more active against gram-positive bacteria than some other members in its class. A methoxy group at position 8 conferred good anaerobic activity. Better intracellular penetration was created, on a par with the macrolides, but surpassing the β-lactams in usefulness when pathogens are intracellular. Due to their rapid bactericidal, as opposed to bacteriostatic, effect on microbes, the fluoroquinolones became important antibiotics for the treatment of serious infections, especially among elderly people and those with diminished immune capacity, rivalling the β-lactams in clinical importance in only 2 short decades.[5]

Today, fluoroquinolones have earned an indisputable place in the treatment of a wide variety of systemic infections and are recommended as alternate drugs of choice for infections caused by *S aureus* and *S epidermidis*, both methicillin-susceptible and methicillin-resistant strains. In vitro activity against most *S pneumoniae* is excellent, including penicillin- and cephalosporin-resistant strains. Moxifloxacin is also recommended for the treatment of infections caused by *S pneumoniae* that is penicillin-susceptible or has intermediate resistance, and may be included as a drug of choice for infections caused by these organisms with high-level penicillin resistance. The fluoroquinolones are

Figure 1. The evolution of the fluoroquinolones.



recommended as treatment against several enteric gram-negative bacilli including *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Serratia* spp, and against *H influenzae*, as well as *Enterococccus* spp causing uncomplicated urinary tract infections. The fluoroquinolones are also effective against, and are alternate drugs of choice for, the atypical pathogens, *Mycobacterium tuberculosis* and *Chlamydophila* infections.[21]

Selection of Antibiotics for Ophthalmic Infections

The indicators of clinical success, as described above, against microorganisms causing systemic infections may offer useful guidelines to ophthalmologists for the management of ocular infections when data relating to ocular isolates is less readily available. Moreover, bacteria colonising the face, nasal passages, and adjacent tissues may also affect the bacterial flora surrounding the eye.

In Part I of this article, the changing trends in the microbial flora causing ocular infections throughout Asia and other parts of the world, as well as cultural factors unique to the region that may influence patient outcome, were described. One must bear in mind that the majority of Asia's socio-economic distribution is in rural areas, where modest medical health care delivery systems often do not have facilities for specific identification of causative infectious organisms. Eye care practitioners usually rely on typical or pathognomonic clinical presentations for making educated guesses as to aetiology. This, in addition to the possibility of multi-organism infection, underscores the need for antimicrobial agents that will be effective against most, if not all, of the potential pathogens. Many of the antibiotics once relied on for ophthalmic care in the Asian region are now becoming outdated for a variety of reasons.

Disadvantages of Older Antibiotics in Ophthalmology

The clinical usefulness of the older ophthalmic antibiotics is fading because of limitations in the spectrum of activity, bacterial resistance, and unwanted adverse effects. Bacterial susceptibility to sulfacetamide has decreased during recent years and it may be sensitising in some individuals, on rare occasions causing Stevens-Johnson syndrome. Neomycin has a limited spectrum of activity and causes local sensitivity reactions in approximately 5% to 10% of patients. Chloramphenicol has been associated with rare cases of aplastic anaemia, even from topical administration, and its mechanism of action is bacteriostatic rather than bactericidal. However, outside of the USA, chloramphenicol is still commonly used, primarily because of its economical cost. The aminoglycosides gentamycin and tobramycin have poor in vitro efficacy against most streptococci. Bacitracin and erythromycin are not active against the gram-negative microorganisms causing ophthalmic infections and polymyxin B has activity only against gram-negative organisms, but is poorly effective.[22-25]

In the past, truly broad-spectrum topical antibiotics for ocular infections were unavailable, and sufficiently potent formulations often required 2 different antibiotics and extemporaneous formulation to fulfil clinical needs.[25] The newer fluoroquinolones have evolved through methodical, stepwise research to produce compounds that are broad spectrum, clinically useful, and effective.

Moxifloxacin 0.5% Ophthalmic Eye Drops

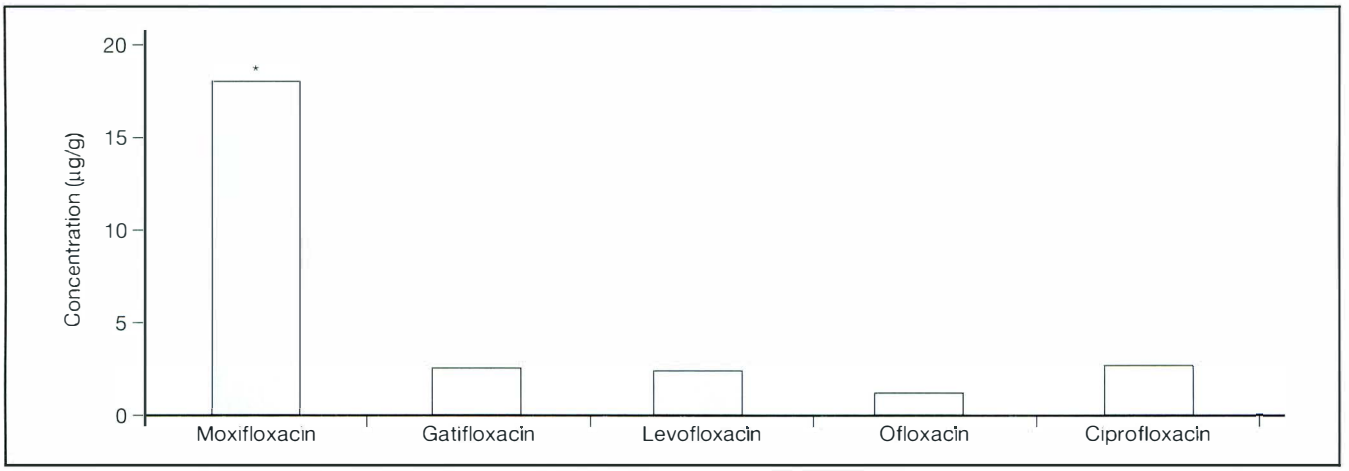
The great contribution of the fourth-generation fluoroquinolones, which includes moxifloxacin, was the dramatic improvement in activity against most gram-positive bacteria, while retaining much of the activity against gram-negative bacteria seen with the older fluoroquinolone, ciprofloxacin. In addition, many strains that had become resistant to earlier fluoroquinolones now showed good susceptibility to moxifloxacin, with anaerobes also being more susceptible.[5,26,27] In 2006, an ophthalmic eye drop preparation of moxifloxacin was commercially launched in Japan, the first to be available in the Asian region. As a fourth-generation fluoroquinolone antibiotic, moxifloxacin 0.5% ophthalmic solution is evolving as a standard of care for many treatment and prophylactic regimens, and may play an important role against the broad range of ocular infections described in Asian populations.

Moxifloxacin 0.5% is a new fourth-generation fluoroquinolone antibiotic, available in ophthalmic drop form (Vigamox®), that exhibits a broad spectrum of antimicrobial action against the majority of important ocular pathogens, including gram-positive and gram-negative bacteria, anaerobes, and atypical mycobacteria. Drug penetration to ocular tissues after topical administration (from eye drops) produces effective antimicrobial levels with a high degree of safety to the eye. Moxifloxacin has a bactericidal mechanism of action, as opposed to a bacteriostatic mechanism. In bacterial keratitis[26] and/or endophthalmitis isolates,[27,28] moxifloxacin has demonstrated increased efficacy against gram-positive microbes and especially against *S aureus* isolates resistant to older fluoroquinolones such as ciprofloxacin, levofloxacin, and ofloxacin, while still maintaining good efficacy against gram-negative bacteria.

Ocular Safety

The safety of moxifloxacin to ocular tissues is well documented.[29-32] Vigamox eye drops are compatible with ocular tissues, being isotonic, with osmolality of 290 mOsm/kg and a pH near 6.8.[33] Vigamox

Figure 2. Conjunctival concentrations of ophthalmic fluoroquinolones.
* $p < 0.001$.



is sterile and self-preserved, eliminating the need for added preservatives that are known to have toxic effects on the corneal epithelium.[34,35]

A study of endothelial and epithelial cell counts and tear break-up time after 1 drop of moxifloxacin administered 4 times daily for 3 days in volunteers resulted in no significant differences between treated eyes and fellow control eyes.[29] No effects on visual acuity or ocular surface integrity were noted. Furthermore, in eyes with an epithelial defect, healing rates were significantly better in eyes treated with moxifloxacin after photorefractive keratectomy than in eyes treated with topical gatifloxacin drops.[32]

Ocular Penetration and Efficacy

Effective antimicrobial action is closely tied to the peak concentrations achievable, as high levels are associated with higher degrees of bacterial kill. When compared with other available topical fluoroquinolones, moxifloxacin shows favourable penetration characteristics.

Comparisons of conjunctival concentrations of 5 ophthalmic fluoroquinolones after instillation of a single eye drop showed that moxifloxacin attained concentrations 6 to 15 times higher than the other 4 agents tested ($p < 0.001$; Figure 2).[36] This indicates that moxifloxacin has excellent tissue penetration characteristics, with both hydrophilic and lipophilic, or biphasic, characteristics. High concentrations in the conjunctiva support the efficacy of moxifloxacin for the treatment of infectious conjunctivitis.

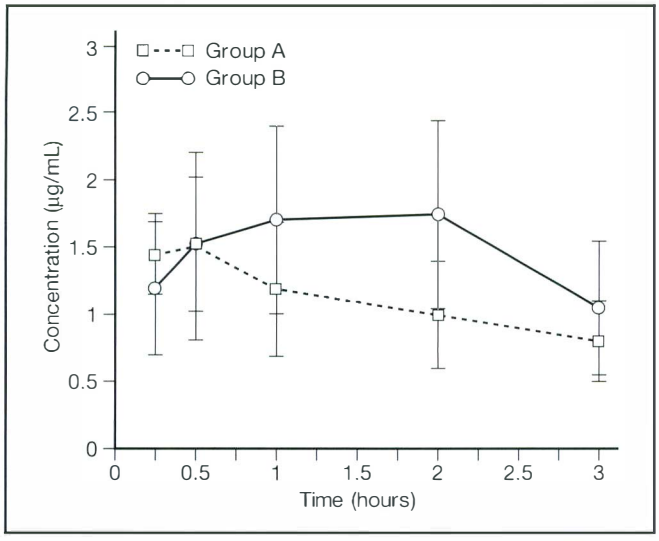
Corneal penetration of moxifloxacin was measured after instillation of 2 preoperative drops given 5 minutes apart. Moxifloxacin reached mean peak levels of 48.5 μg/g in corneal stroma, approximately 3 times higher than levels after gatifloxacin drops administered the same way. These peak levels of moxifloxacin were approximately 12 to 800 times higher than the minimal bactericidal concentration$_{50}$ (MBC_{50}) for *S aureus*, *S epidermidis*, *P aeruginosa,* and *Serratia marcescens*.[37]

Penetration into aqueous humour after topical eye drop administration has relevance for preoperative prophylaxis of endophthalmitis. While levels achieved in aqueous humour are generally lower than those in corneal stroma, after multiple eye drop administration effective levels may penetrate to the aqueous humour. A number of eye drop regimens have been evaluated clinically. Moxifloxacin was instilled in 1 of 2 regimens for patients with cataract, as follows:[38]

- group A — 1 drop every 15 minutes for 4 doses before surgery
- group B — 1 drop 4 times daily on the day before surgery plus the regimen of group A.

Patients were randomised so that the last dose was administered 0.25, 0.50, 1, 2, or 3 hours before aqueous humour sampling. The results showed that moxifloxacin was well absorbed into the aqueous humour, reaching levels >1 μg/mL within 15 minutes (Figure 3). While there was no statistically significant difference in mean peak levels between the 2 treatment groups, there was a higher overall drug concentration over time (area under the curve$_{0\text{-}3h}$) in the group receiving the combination treatment regimens. A different eye drop regimen of 1 drop every 10 minutes for 4 doses beginning 1 hour prior to surgery compared the aqueous humour levels after preoperative administration of moxifloxacin 0.5% or gatifloxacin 0.3%.[39] Mean aqueous humour peak levels for moxifloxacin reached 1.8 μg/mL (SD, 1.21 μg/mL), levels that were 3.8 times higher than those for gatifloxacin. In a report from Hong Kong, application of 1 drop of moxifloxacin 0.5% every 10 minutes for 1 hour before cataract surgery produced aqueous humour levels of 1.576 μg/mL (SD, 0.745 μg/mL).[40] Comparable levels (1.86 μg/mL [SD, 1.06 μg/mL]) were also found in a USA study after 1 drop was given 4 times daily on the day before surgery with an additional drop 1 hour before surgery.[41]

Figure 3. Mean aqueous humour concentrations of moxifloxacin as a function of time.
Group A regimen — 1 drop every 15 minutes for 4 doses before surgery.
Group B regimen — 1 drop 4 times on the day before surgery plus the regimen for group A.



Most recently, use of the moxifloxacin ophthalmic solution by direct intracameral injection has also been explored for prophylaxis for endophthalmitis, without apparent adverse effects.[42-44] As microorganisms may linger in the surgical field or enter the eye near the close of cataract surgery through wound imperfections, effective antibiotic coverage throughout the perioperative period is beneficial. Anterior chamber contamination rates of 5% to 43% have been reported after routine cataract surgery.[45-47] One recent study in Japan also examined the stepwise changes in ocular surface contamination from 1 week preoperatively to intraoperatively.[5] Despite preoperative eye drops and use of surgical scrubs, microbes were still isolated from the conjunctiva and ocular fluids, showing a relative rise in the proportion of *Propionibacterium acnes* during this period. This study pointed out that complete sterilisation of the ocular surgical field may not be possible and that *P acnes*, commonly implicated in late onset endophthalmitis, was still present on the ocular surface in the midst of the operation itself. These findings emphasise the need for delivery and maintenance of effective antibiotic levels throughout the surgical period.

Antibacterial Efficacy and Bacterial Resistance in Ocular Isolates

The delivery of effective antibiotic levels to targeted ocular tissues is fundamental to a therapeutic outcome. Antimicrobial efficacy is measured by parameters such as the minimal inhibitory concentration (MIC) and the MBC. The mutant prevention concentration describes a level sufficiently high to retard the development of intrinsic resistance in microbial organisms. Although the MIC is the common standard for infections outside the eye, where host immune responses play a major role, ocular infections are unique in that targeted areas are often poorly vascularised and separated by tissue barriers from the systemic circulation. Therefore, the MBC has greater relevance when discussing antimicrobial effectiveness in ocular infections.[48-52] The MBC_{50} of moxifloxacin against important ocular pathogens in corneal stroma and aqueous humour is shown in Figures 4 and 5.[53]

Figure 4. Minimal bactericidal concentration$_{50}$ of moxifloxacin in corneal stroma.
* Fluoroquinolone-sensitive pathogens.

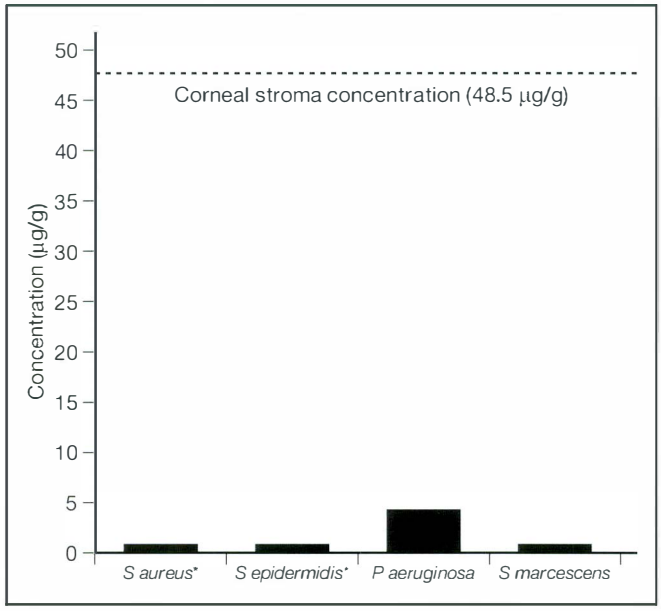
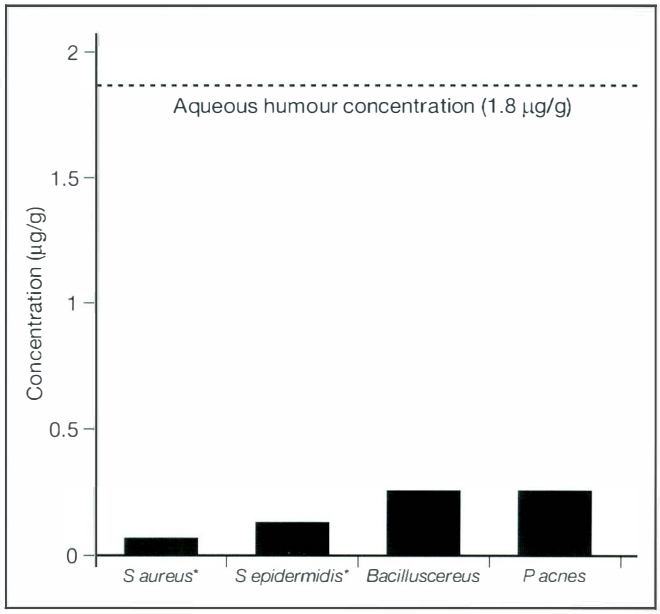


Figure 5. Minimal bactericidal concentration$_{50}$ of moxifloxacin in aqueous humour.
* Fluoroquinolone-sensitive pathogens.



One aspect of antibiotic treatment unique to ocular infections involves the principle that high concentrations of antibiotic, relative to the MIC or MBC, are delivered via topical drops and alternative dosing regimens. These regimens deliver antibiotic levels to ocular tissues that are often several multiples above the MIC or MBC determined by laboratory measurements. As a result, a better than expected clinical response is often seen.[24,54] However, one study showed that when staphylococcal isolates from bacterial keratitis were resistant in vitro to ciprofloxacin, the clinical response was also weaker than when isolates were susceptible.[55]

Nevertheless, high concentrations of antibiotic may be more effective clinically than anticipated from laboratory sensitivity data, and are also thought to retard development of bacterial resistance. As mentioned above, one should keep in mind that local antibiotic administration to the eye, whether via topical, subconjunctival or intracameral routes, delivers extremely high concentrations of antibiotic that far exceed reference levels used in sensitivity testing that refers to levels achieved in serum. The newer fluoroquinolones seem to have a lower rate of development of mutant strains of bacteria. Their enhanced antimicrobial action is due to the targeting of both the microbial DNA gyrase and topoisomerase IV, whereas older compounds targeted only a single step mutation.[5]

In one European report, the newer quinolones showed better activity against gram-positive organisms and anaerobes, with similar activity against gram-positives organisms.[56] Activity against *S pneumoniae* and *Enterobacteriaceae* was less reliable, although moxifloxacin was more active against *S pneumoniae* and *S aureus* than levofloxacin, gatifloxacin, and gemifloxacin. Resistant subpopulations emerged after exposure to levofloxacin and gatifloxacin, but not to moxifloxacin. Emergence of resistance was noted to be tied to both achievable drug concentrations in vivo and microbial resistance patterns. The authors suggested that the use of more potent fluoroquinolones, in effective concentrations, should be used as first-line agents to preserve the potential of this class of compounds and to provide the best treatment regimens.

Conclusions

In Part I, and this Part II of this series, the changes in bacterial resistance patterns throughout Asia, the shifting trends in the epidemiology of ocular infections, and the cultural factors that pose unique challenges for health care workers have been reviewed. Better access to effective and safe topical antibiotics has been cited as a primary factor for improving patient outcomes and quality of life. These challenges point to the need for a broad-spectrum antibiotic, with greater antibacterial efficacy than older, traditionally used agents, one that can be applied safely in a variety of dosage regimens to deliver effective antibiotic levels to the eye. In many regions, moxifloxacin 0.5% ophthalmic solution is evolving as a standard of care for treatment and prophylactic regimens. This series has described the targeted evolution of the new fourth-generation fluoroquinolone antibiotic, moxifloxacin, and has examined its unique characteristics and applicability for the management of ocular infections throughout the changing landscape of Asia.

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Endoilluminator-assisted Technique for Visualisation of Vitreous during Anterior Vitrectomy

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This report describes a simple and effective technique for visualising the vitreous during automated vitrectomy. In this technique, an endoilluminator is used for visualisation of vitreous strands. The vitrectomy is performed as a closed chamber technique, with the microscope lights switched off. The endoilluminator is held near the limbus as an external light source. The authors consider this technique to be an important tool for teaching residents how to manage vitreous loss in cataract surgery, primary posterior capsulotomy, and anterior vitrectomy in paediatric patients.

Key words: *Anterior chamber, Cataract extraction, Intraoperative complications, Lighting, Vitrectomy*

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Introduction

Cataract is the most common ophthalmic operation performed worldwide; as many as 4 million surgeries are performed each year.[1] Intraoperative complications are inevitable, even when experienced surgeons perform the operation. Proper management of intraoperative complications is key to a good postoperative outcome comparable with uneventful surgery.

The most common intraoperative complication of cataract surgery is vitreous loss, with a reported prevalence of 1% to 7%.[2,3] The prevalence rate increases when the surgery is performed by residents rather than experienced surgeons.[4] The proper management of vitreous prolapse by automated vitrectomy can prevent associated postoperative complications such as cystoid macular oedema, retinal detachment, or endophthalmitis, all of which eventually lead to a poor visual outcome.[5]

The limiting step in any vitrectomy is visualisation of the transparent, and often invisible, vitreous strands that prolapse into the anterior chamber or within the wound area. This visualisation with a surgical microscope is difficult, even with retroillumination, and becomes harder if viscoelastic or lens fragments are admixed. Experienced surgeons can determine vitreous only by indirect means; by assessing distortions in the shape of the pupil and tug on the iris. Similarly, the end point of the vitrectomy is equally difficult to determine, since indirect clues such as iris-tug may be absent, but the vitreous humour may still be in the anterior chamber. In such a situation, clinicians need a special device that is not only inexpensive, but also easily accessible and can be used without additional expertise. This report describes a simple technique that is an effective and easy way to visualise the vitreous. The technique not only hastens evacuation of the vitreous from the anterior chamber by experienced surgeons, but also ensures complete removal by inexperienced surgeons.

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Technique

The aim of this technique is to 'localise the otherwise transparent vitreous gel', that is to 'see what the others cannot'. The technique is a bimanual closed-chamber mechanical anterior vitrectomy using an endoilluminator for better visualisation, thus enabling easy identification and removal of any residual vitreous.

Indications

There are 3 main indications for this technique, as follows:

- in paediatric cataract surgery during anterior vitrectomy after posterior capsulorrhexis
- when there is vitreous loss during routine cataract surgery, either manual small-incision cataract surgery or phacoemulsification
- for clearing the vitreous from the anterior chamber in aphakic eyes prior to secondary intraocular lens implantation.

The Procedure

The following describes the steps of the procedure. Once vitreous loss has occurred, further manipulation through the main wound

should be avoided. Two 20-G paracentesis are made using the myringotome (Mani Ophthalmics, Tochigi, Japan), one at the infero-temporal location and the second at the 10 o'clock position (Figure 1). An anterior chamber maintainer (BD Visitec, Franklin Lakes, USA) is introduced through the infero-temporal side port (Figure 2). The ocutome or automated vitreous cutter (Millenium; Bausch & Lomb, Rochester, USA) is introduced at the 2 o'clock or 10 o'clock port (Figure 2). The endoilluminator (Carl Zeiss, Jena, Germany) is held externally by the surgeon or assistant at the limbus, after presterilisation by ethylene oxide. The position of the endoilluminator can be altered along the limbus to verify a precise vitreous clean up (Figure 3). Standard anterior vitrectomy is then performed, with a cutting speed of 600 strokes per second.

The procedure is performed with more efficiency with the room lights and microscope lights switched off. Normally, under the diffuse light of the microscope or even retroillumination the vitreous fibrils are not evident (Figure 4), but they can be clearly delineated by adjustment of the oblique light of the endoilluminator as they are cut with the ocutome (Figure 5). The light should be directed towards the cutting port and not onto it.

The endpoint of the procedure is when the anterior chamber is cleared of the vitreous; the vitreous phase lies below the level of the posterior capsule and no more strands are seen entering the cutting port. This technique ensures that the prolapsed vitreous is completely removed from the anterior and posterior chambers with minimum intervention, and avoids excessive surgical manipulation during posterior capsular rupture and vitreous loss, thereby avoiding further possible complications.

Figure 1. The anterior chamber maintainer is in position in the inferotemporal port and the second port at 10 o'clock is for the vitrectomy probe.

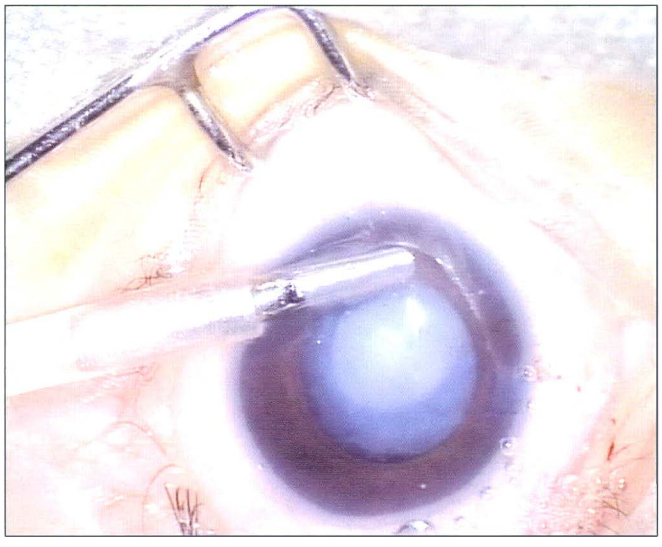
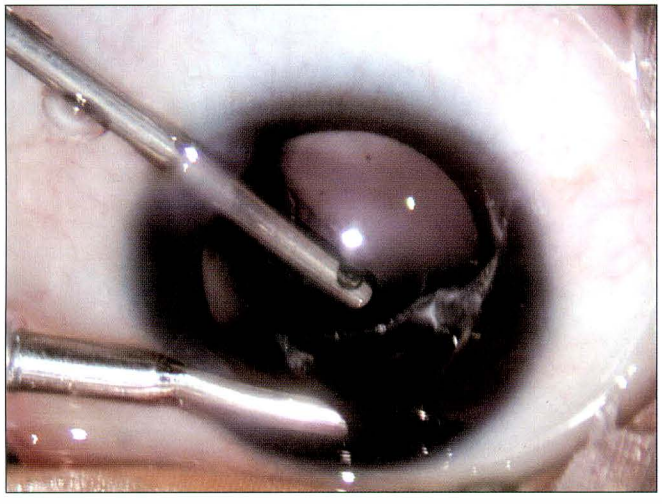


Figure 2. The ocutome and the anterior chamber maintainer are in place.



Discussion

This technique promises to be a significant aid for elective as well as unplanned vitrectomies and for ensuring a thorough clean up

Figure 3. The endoilluminator is held externally at the limbus.

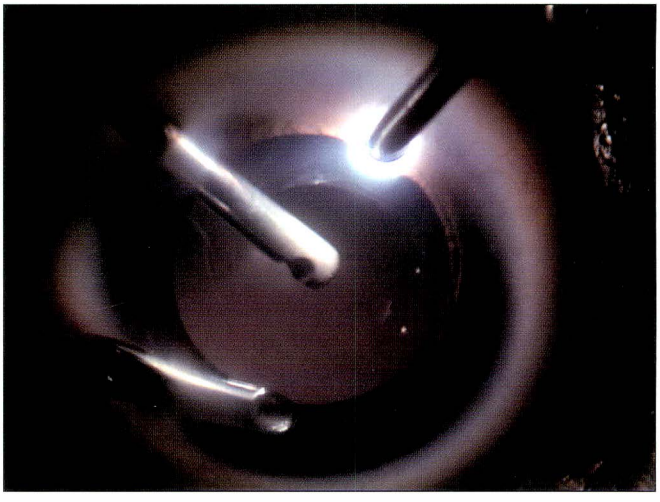


Figure 4. Vitrectomy without the endoilluminator.

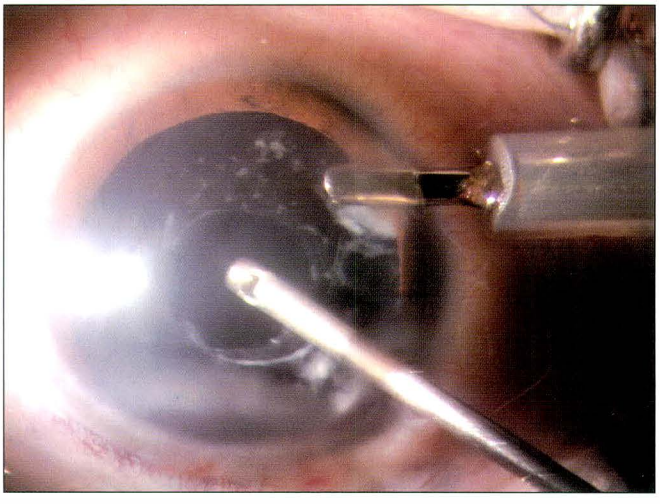
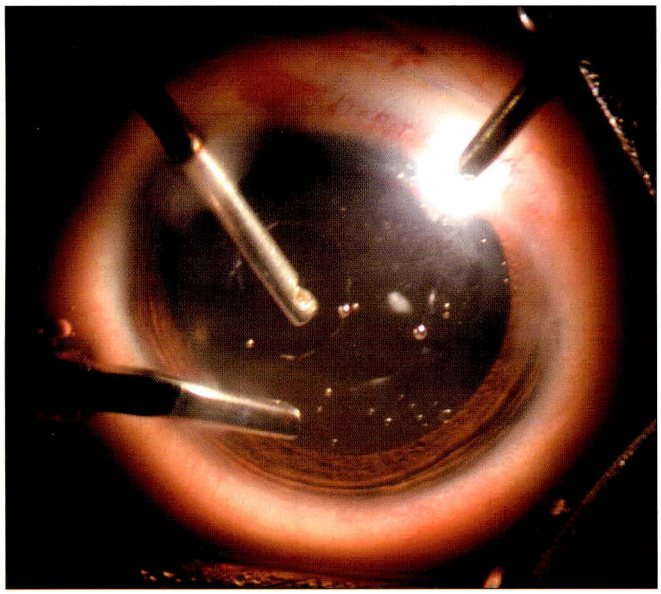


Figure 5. Vitrectomy with the endoilluminator — note that the vitreous strands are now clearly visible. The light is directed obliquely towards the cutting port.



of vitreous. The bimanual closed system has several advantages over the open techniques, including reduced traction on the peripheral retina and maintenance of the anterior chamber and intraocular pressure throughout the procedure, thereby avoiding complications related to ocular hypotension and trauma secondary to instrumentation use.

Other techniques to facilitate visualisation of the vitreous during anterior segment surgeries have been described.[6,7] These techniques require the use of pharmaceutical agents and have their own advantages and disadvantages. Granules of triamcinolone have been used to visualise the vitreous in the anterior chamber after posterior capsule loss,[7] but corneal endothelial damage[8] and steroid-induced glaucoma have been reported after its use. No additional complications related to the technique of endoillumination are expected, and none have occurred to date.

Oyakawa et al reported their experience of the use of an irrigating endoilluminator for anterior vitrectomy.[9] These authors used a May illuminated/infusion needle via a 19-G paracentesis, along with the ocutome. The light was directed towards the cutting port for visualisation. In the technique described here, a non-irrigating endoilluminator was used in conjunction with the anterior chamber maintainer. This avoids the use of an irrigating needle, which not only reduces the cost but also makes the technique easily accessible, as the use of an anterior chamber maintainer can be easily mastered and the use of a specialised endoilluminator is avoided. An endoilluminator can be readily available (it is part of the retina instrumentation at the authors' hospital) although it is not part of a standard cataract set.

One of the authors has been using this technique for more than 12 years and can attest to its ability to visualise the vitreous and remove strands that would otherwise be missed.[5,10] The outcomes, including complication rates, and a comparison with standard techniques have not been analysed by these authors, but a prospective study is underway to assess these factors.

To conclude, irrespective of the cause, any anterior segment vitrectomy could be successfully managed using an endoilluminator in conjunction with an anterior chamber maintainer; a successful outcome can be achieved even by inexperienced surgeons.

Acknowledgement

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Tuberculous Myositis of the Orbit

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A 45-year-old man presented with proptosis of the right eye for 2 months. Computed tomography of the orbit revealed bulky inferior and superior rectus muscles. Fine needle aspiration cytology showed central caseative granuloma suggestive of a tubercular lesion, and Mantoux test was positive. Based on the clinical, laboratory, and radiological findings, a diagnosis of tuberculous myositis was made. After anti-tuberculosis treatment, the proptosis regressed and the patient recovered fully. A search of the literature did not reveal any similar manifestation of orbital tuberculosis.

Key words: *Biopsy, fine-needle, Granuloma, Myositis, Tuberculosis*

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Introduction

Orbital involvement is a rare ocular manifestation of tuberculosis. In India and in other areas where tuberculosis is endemic, orbital tuberculosis is more common.[1] Tests such as tuberculin reaction and fine needle aspiration cytology (FNAC) should be considered among the routine diagnostic investigations. This report emphasises that tuberculosis should be considered in the differential diagnosis of orbital diseases, especially in developing countries where the disease is still common.

Case Report

A 45-year-old man presented in October 2007 with gradually increasing painless proptosis of the right eye for the previous 2 months (Figure 1). He did not have fever, respiratory symptoms, or human immunodeficiency virus.

Ocular examination revealed visual acuity of 6/12 in the right eye and 6/6 in the left eye. He had axial proptosis with upward displacement of the globe, blepharoptosis, chemosis, and congestion of conjunctiva in the right eye. Ocular movement was restricted in all gazes, but more so in downward gaze. There was a prominent infraorbital swelling (25 x 7 mm), which was firm, non-compressible, and non-tender. The anterior segment was within normal limits, cup-disc ratio was 0.6:1 in the right eye and 0.4:1 in the left eye, and intraocular pressure was 33 mm Hg in the right eye and 19 mm Hg in the left eye.

Systemic examination revealed cervical lymphadenopathy on the right side. Routine blood investigations were normal. The Mantoux test showed a zone of induration of 8 mm after 72 hours, sputum tests for acid-fast bacilli for both smear and culture were negative and the chest radiograph was normal. Computed tomography (CT) of the orbit revealed bulky inferior and superior rectus muscles (Figure 2). CT-guided FNAC showed central caseative granuloma suggestive of a tubercular lesion (Figure 3).

The patient was referred to his physician for category 3 anti-tuberculosis treatment of isoniazide (INH) 300 mg, rifampicin 450 mg,

Figure 1. Unilateral proptosis in a 45-year-old man.

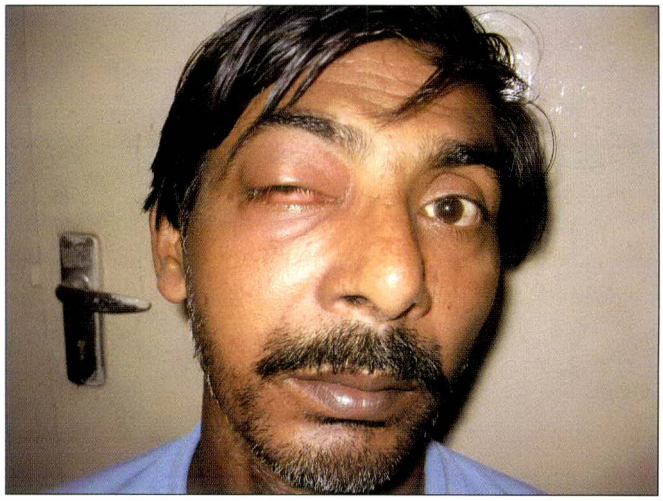

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Figure 2. Computed tomography scan of the orbit showing bulky superior and inferior rectus muscles.

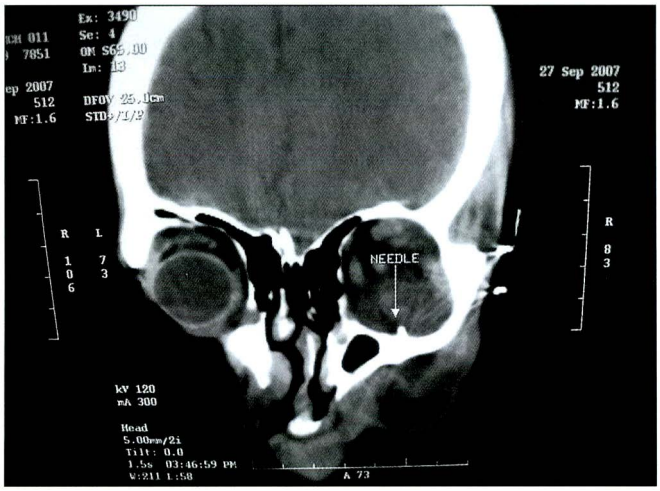
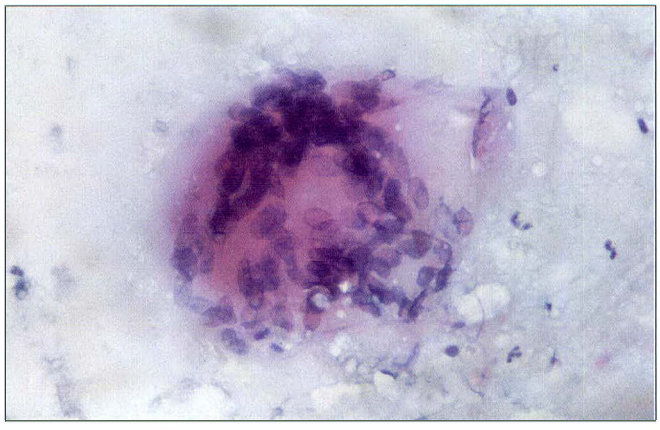


Figure 3. Fine needle aspiration cytology showing inflammatory cells, granulomatous collection of epitheloid cells, giant cells, and caseating necrosis.



and pyrazinamide 1200 mg 3 times per week for 2 months — INH and rifampicin were continued for a further 4 months. Serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase were estimated at 2-monthly intervals and were within normal limits.

At 1-month follow-up, there was a marked reduction of proptosis, his visual acuity was 6/6 in both eyes, IOP was 18 mm Hg in both eyes, and the visual field was normal for both eyes. Orbital CT scan done after 3 months showed complete recovery of the lesion. The patient has recovered well, and has been taking antituberculosis medication for the past 6 months.

Discussion

Orbital involvement is a rare manifestation of tuberculosis. However, the global incidence and prevalence of *Mycobacterium tuberculosis* infection is not yet controlled, and the disease is a serious public health problem.[2] Clinicians must be aware of the possibility of tuberculosis among patients presenting with orbital diseases. Extrapulmonary tuberculosis constitutes approximately 10% of all cases of tuberculosis.[3] Tubercular involvement of the eye in India, where the disease is endemic, is common, but orbital lesions are extremely rare. Agarwal et al have reported 14 patients with orbital involvement in tuberculosis from India.[4] Ocular infection may be evident in 2 forms: the tubercle bacilli may arrive in the orbital region by haematogenous spread from the primary site, which can lead to periostitis of the orbital margin or tuberculoma of the orbital tissue, or by direct extension from neighbouring structures.[4] Both ocular and orbital tuberculosis are usually unilateral.[5]

The most common clinical manifestations of orbital tuberculosis are insidious and progressive unilateral proptosis, a cold, painless eyelid swelling, chemosis, and conjunctival hyperaemia. There may also be involvement of the ocular muscles.[2] In this patient, both the inferior and superior rectus muscles were involved.

The differential diagnosis of orbital tuberculosis includes diseases that cause unilateral proptosis. In adults, pseudotumour of the orbit, lymphoma, and cavernous haemangioma should be considered.[6] It may not be possible to demonstrate primary tuberculosis on radiological examination;[4] CT-guided FNAC suggested the diagnosis for this patient.

It is known that acid-fast bacilli are difficult to detect in pathological specimens and the diagnosis is usually based on the following:

- positive tuberculin test
- a caseating granulomatous inflammatory lesion by histopathology or by orbital FNAC, which is highly suggestive of active tuberculosis
- positive culture for mycobacteria
- complete resolution of the disease with antitubercular medication.[7]

A definitive diagnosis of tuberculosis is often elusive because it requires the demonstration of *M tuberculosis* in ocular tissues or secretions by microscopy or culture.

Biopsy is not practical for most ocular diseases, and the difficulty of isolating the organisms and the extreme variability of ocular manifestations makes routine clinical diagnosis difficult. The similarity of the lesion to other granulomas adds to the diagnostic challenge. Other possible causes of granulomatous inflammation, including syphilis, brucellosis, toxoplasmosis, toxocara, and sarcoid, must be ruled out.[8]

This patient emphasises the importance of vigilance for tuberculosis, especially in developing countries. Due to the increase in the prevalence of tuberculosis because of human immunodeficiency virus, clinicians should be aware of this possible aetiology when managing orbital diseases. Despite the difficulties in diagnosis, the treatment for tuberculosis is relatively effective and cost-efficient.

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Concurrent Leiomyosarcoma and Basal Cell Carcinoma of the Conjunctiva

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This report is of the synchronous occurrence of conjunctival leiomyosarcoma and basal cell carcinoma. A 74-year-old, otherwise healthy, man presented with a sessile fleshy nodular conjunctival lesion of 4 months' duration, located at the nasal limbus of the left eye. No associated cutaneous lesions were present. The growth was approximately 7.0 x 5.0 x 2.5 mm, and extended over the adjacent cornea to the pupillary area. Excision of the growth with cryotherapy to the underlying scleral bed was performed. Histopathological evaluation of the excised mass revealed evidence of basal cell carcinoma and leiomyosarcoma. The cells showed strong expression of smooth muscle actin and were negative for melanocytic and epithelial markers (S-100 protein, HMB45, and cytokeratins).

Key words: *Carcinoma, basal cell, Leiomyosarcoma*

Asian J Ophthalmol. 2008;10:401-3

Introduction

The most common conjunctival mass causing corneal blindness in countries with an arid dry hot climate is a pterygium. Lesions that may clinically resemble a pterygium include benign and malignant tumours such as choristomas, and squamous cell and basal cell carcinomas.[1-4] Primary basal cell carcinomas of mucosal surfaces, particularly the conjunctiva, are rare with only 4 reported in the past 20 years.[1-9]

Four of every 1 million people develop leiomyosarcoma, which can affect the lungs, liver, blood vessels, or other soft tissues of the body. A benign leiomyoma and an isolated leiomyosarcoma of the conjunctiva have been identified[10] but, to the authors' knowledge, the occurrence of leiomyosarcoma of the conjunctiva in conjunction with a basal cell carcinoma has not been observed to date.[6-13]

Case Report

A 74-year-old man presented with a history of a slow-growing painless mass in his left eye for 4 months. His right eye had been amblyopic. He gave no history of trauma or systemic illness.

At examination, the best-corrected visual acuities were -2.50/-1.25/170° = 0.1 in his right eye and hand movements in his left eye. External ocular examination revealed a fleshy mass, approximately 7.0 x 5.0 x 2.5 mm, attached to the nasal conjunctiva by a broad-based peduncle. The mass extended across the limbus, overhanging the adjacent cornea, and covering the pupillary area. The surface of the mass was nodular and showed dilated blood vessels. Appositional closure of the lids in the left eye was defective due to the mass. The temporal conjunctiva and adjacent cornea appeared desiccated. Plica semilunaris and caruncle were normal. There was a nuclear cataract in his right eye and trachomatous scarring of the conjunctiva and cornea in both eyes, which was worse in the left eye than in the right eye. Intraocular pressure in the right eye was 12 mm Hg, but this could not be assessed in the left eye due to the mass. Extraocular muscle movements were normal. Fundus examination in the right eye was normal. The fundus of the left eye could not be evaluated due to corneal scarring and the overhanging mass. B-scan ultrasound examination of both eyes revealed normal posterior segments. Systemic examination was unremarkable, and there was no localised or generalised lymphadenopathy.

Laboratory investigations reported a normal blood count. Serology was negative for retrovirus, cytomegalovirus, and herpes simplex virus. CD4 cell count was 0.9 x 10^9/L (normal range, 0.5-1.3 x 10^9/L) and CD8 cell count was 0.6 x 10^9/L (normal range, 0.3-1.0 x 10^9/L). Liver function and renal function tests were normal. Stool tested negative for occult blood. Abdominal ultrasound and chest X-ray were normal. Mantoux test was negative. Computed

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cranial tomography showed no intraocular, orbital, or intracranial extension of the growth.

The tumour was excised by superficial lamellar keratectomy on the corneal side and superficial lamellar sclerectomy on the scleral side, with margins of 1 mm and 2 mm, respectively. Cryotherapy was applied (-80°C for 60 seconds) to the tumour bed.

Histopathological evaluation showed evidence of coexisting basal cell carcinoma and leiomyosarcoma. Haematoxylin and eosin stain showed thinning of the epithelium and downward extension of basaloid cells in strands with peripheral palisading of the nuclei, interspersed with keratin cysts (Figure 1).

Epithelial parakeratosis, basal cell proliferation, nuclear atypia, loss of polarity, and occasional mitoses due to solar elastosis were noted in the basal layers of the conjunctiva. There was basophilic degeneration of the subepithelial collagen. The stroma showed a mucoid degeneration suggesting a basal cell carcinoma. Areas of the tissue also showed neoplastic spindle-shaped cells (Figure 2). The resection margin was clear of tumour cells.

Immunoperoxidase staining revealed an unencapsulated nodular lesion with indistinct margins composed of spindle cells with oval nuclei, and typical cytoplasmic fibrils without necroses. Nuclear atypias, giant cells, and 4 to 6 mitoses/10 high-power fields were noted. These cells showed a strong expression of smooth muscle actin suggesting leiomyosarcoma (Figure 3). The tumour stained negative for melanocytic and epithelial markers (S-100, HMB 45, and cytokeratin), human papillomavirus or Epstein-Barr virus, and human papillomavirus DNA on in situ hybridisation. Alterations of bcl-2, c-erb-b2 and Rb oncoproteins were not found immunohistochemically. Overexpression of p53 was detected by immunohistochemistry in both tumours, but p53 gene mutations were not found by polymerase chain reaction. Local recurrence was noted after 3 years.

Figure 1. Histopathology showed evidence of coexisting basal cell carcinoma and leiomyosarcoma, with thinning of the epithelium and downward extension of basaloid cells in strands with peripheral palisading of the nuclei, interspersed with keratin cysts (haematoxylin and eosin stain; original magnification, x 100).

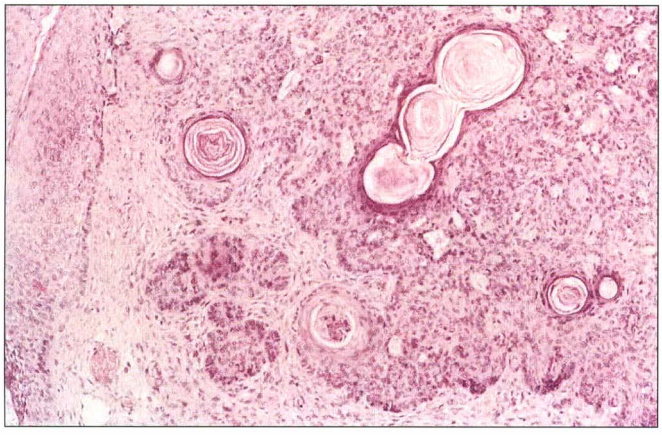


Figure 2. Epithelial parakeratosis, basal cell proliferation, and nuclear atypia, loss of polarity and occasional mitoses due to solar elastosis was noted in the basal layers of the conjunctiva. There was basophilic degeneration of the subepithelial collagen. The stroma showed a mucoid degeneration suggesting a basal cell carcinoma. Areas of the tissue also showed neoplastic spindle-shaped cells, which were better appreciated at higher magnification (haematoxylin and eosin stain; original magnification, x 200).

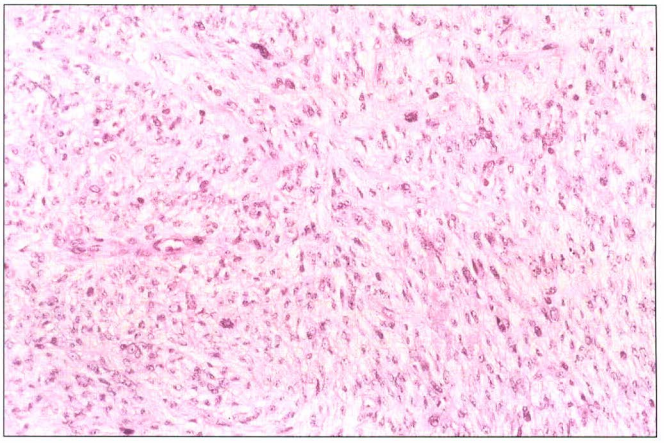
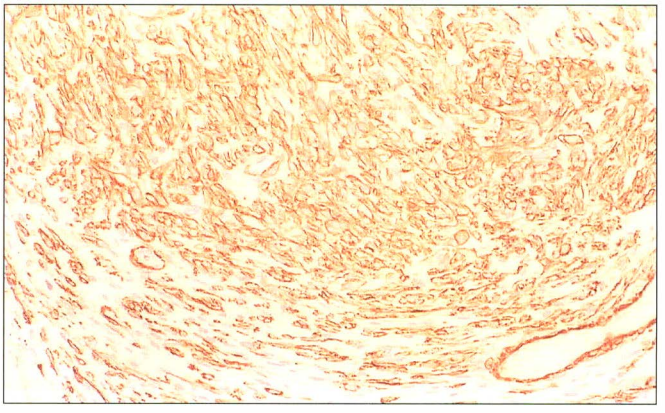


Figure 3. Immunoperoxidase staining revealed an unencapsulated nodular lesion with indistinct margins composed of spindle cells with oval nuclei, and typical cytoplasmic fibrils without necroses. Nuclear atypias, giant cells, and 4 to 6 mitoses/10 high-power fields were noted. These cells showed a strong expression of smooth muscle actin suggesting leiomyosarcoma (original magnification, x 200).



Discussion

This report describes an elderly patient with a slow-growing conjunctival mass composed of a low-grade leiomyosarcoma and a basal cell carcinoma, which extended to the cornea. Basal cell carcinomas originating from the basal layer of the nasal limbal conjunctival epithelium have been reported previously.[1-9]

Ash and Wilder initially observed 1 patient with basal cell carcinoma in a series of 93 patients with corneoscleral epithelial tumours.[4] Later, Ash reported 53 patients with basal cell carcinoma in a series of 1120 patients with epibulbar tumours.[5] However, it is not clear whether these lesions were extensions from adjacent adnexal structures or had developed primarily from the conjunctiva. Aftab and Percival,[6] Apte et al,[7] and Hussein et al[8] reported the

occurrence of a primary basal cell carcinoma as a fleshy growth on the nasal interpalpebral conjunctiva. None of the lesions were invasive. Complete excision of the lesions was performed, and none recurred.

Cable et al reported a morpheaform type of basal cell carcinoma originating from the basal layer of the nasal limbal conjunctival epithelium with intraocular extension and secondary glaucoma.[9] The patient in this report had no evidence of intraocular, intraorbital, or intracranial extension.

The most important risk factor for basal cell carcinoma is ultraviolet (UV)-B irradiation, which is unavoidable in the desert country of Oman, and may have been a risk factor for this patient as histopathological features of solar elastosis were evident. A range of 30% to 50% of basal cell carcinomas have been found to express UV-specific mutations in p53 tumour suppressor genes.[1-9] The tumour tested negative for p53 mutations in this patient, but p53 appeared to be overexpressed. A possible facilitation of tumour development involving infection with human papillomaviruses 16 and 18 and immunosuppression has been postulated.[11,12] However, no human papillomavirus infection was detected in this patient, who was also HIV-seronegative.

Primary basal cell carcinomas of the conjunctiva are rare. The lesions tend to occur in older individuals, in the actinically exposed areas of the interpalpebral conjunctiva. The lesion can be locally invasive and destructive, but usually does not metastasise. Local recurrence may occur, as in this patient.[1-9]

Leiomyomas are mesenchymal tumours of smooth muscle origin. In the conjunctiva, leiomyomas and leiomyosarcomas are rare occurrences, originating from either the pluripotent germ cells of the epithelium or the smooth muscle layer of the conjunctival blood vessels.[10,13] No distant metastasis was noted in this patient.

Three rare features are presented in this report — primary basal cell carcinoma of the conjunctiva (4 patients reported in the past 20 years[6-9]), leiomyosarcoma of the conjunctiva (1 patient reported[10]), and the simultaneous occurrence of both tumours (no patients reported to the authors' knowledge). The need for curative removal of epithelial tumours and histopathological examination of the conjunctival masses is highlighted to show the malignant potential, so that patients can be counselled accordingly.

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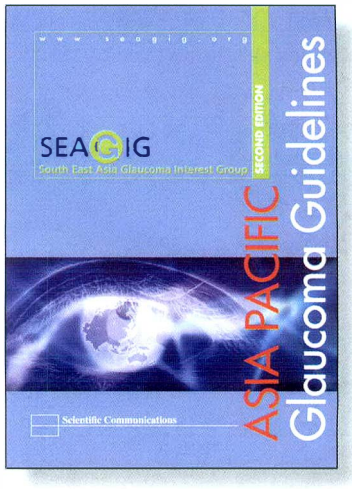
SEAGIG
South East Asia Glaucoma Interest Group

Asia Pacific Glaucoma Guidelines
Second Edition



The second edition of the Asia Pacific Glaucoma Guidelines (APGG2) was launched at the joint SEAGIG/AACGC meeting in Seoul, Korea, on 26 September 2008, almost 5 years after the launch of the first edition in Bangkok, Thailand, in November 2003. To update the guidelines, members of the Working Group met on several occasions to discuss the amendments required and worked closely with the Extended Working Group to provide the most up-to-date information. The updated text was then appraised by the International Review Committee.

The APGG2 are structured in a similar way to the first edition of the APGG, with a brief introduction to *Epidemiology of Glaucoma in Asia*, followed by Section 1: *Assessment*, Section 2: *Treatment*, Section 3: *Follow-up*, and Section 4: *Appendices*. A new chapter *Frequently Asked Questions* has been added to Section 3: *Follow-up*. The goal was to retain a straightforward user-friendly accessible series of resources for Asian ophthalmologists, taking into account the diversity of the region and cultural and ethnic differences. The bullet point format is intended to make the information clear for readers whose first language is not English.

Improvement and Expansion

Each chapter of the APGG2 has been improved and expanded. The chapter on *Epidemiology of Glaucoma in Asia* shows the importance of the disease in the SEAGIG region, which is a diverse area with great variation in genetic and environmental factors. Angle closure rates vary throughout the region, but are much higher in Asia than in the rest of the world. Glaucoma management in the region needs to accommodate this diversity.

Improvements to the chapter on *Patient Assessment* include a new optic disc examination flowchart, a table of percentile values for cup-disc ratio according to disc size, new data for disc haemorrhage, and information from the World Glaucoma Association consensus on optic disc imaging.

The next chapter is *Risk Categories and Treatment Targets*, which aims to enable clinicians to categorise patients according to their risk for visual impairment from glaucoma, and to individualise the treatment targets. The chapter has been updated to include a table of risk factors for glaucoma development and progression. Target pressure can be set according to risk category, and several ways in which target pressure can be used in clinical practice are listed.

The chapter on *Initiation of Treatment* has been updated to include redefined mechanisms that elevate intraocular pressure and simplified mechanisms for angle closure, which are highlighted in one of the many boxed sections. The question of when to initiate treatment has been expanded according to the risks for progression or for conversion to glaucoma. Additional information on treating the mechanisms of glaucoma has been included.

The chapter on *Medical Treatment* remains a cornerstone of the guidelines, and has been reformatted to increase the user-friendliness of the information provided. This chapter is presented in a comprehensive format for easy reference in the office.

The main addition to the chapter on *Laser Treatment* is a section on laser suture lysis. Other improvements include placement of the laser parameters in boxed sections for ready reference; importantly, the laser parameters are modified for Asian eyes. Information about selective laser trabeculoplasty (SLT) has been included, with a table highlighting the differences between SLT and argon laser trabeculoplasty. The indications for iridotomy have been modified.

The *Surgery* chapter includes updated information on the use of antimetabolites and complications of glaucoma drainage device surgery. A new section on non-penetrating surgery has been added, as well as a section on lens extraction for angle closure glaucoma.

In the chapter on *Follow-up*, the aims of follow-up have been expanded, and the process now includes retinal nerve fibre layer imaging as this is becoming more widespread within the region. There is a new table to show the timing of follow-up according to the extent of damage. Quality of life issues are discussed and a new Appendix has been added to show the Glaucoma Quality of Life–15 questionnaire.

The chapter on *Screening* has been updated to include clear definitions of screening terms, a table to show the differences

between screening and diagnosis, and key examination techniques for glaucoma screening. The title of this chapter has changed from *Case Detection* in the first edition, in line with the new information offered.

Frequently Asked Questions is a new chapter, which has been designed to answer the most important questions about glaucoma. The questions are based on each of the chapters in the guidelines. Some of the answers may be controversial as they address topical issues, but may stimulate further debate.

There are several new *Appendices* covering treatment of childhood glaucoma; treatment during pregnancy and lactation; systemic medications that may induce angle closure; principles of management of secondary glaucoma; examples of imaging devices; and the Glaucoma Quality of Life–15 questionnaire. The pre-existing appendices have been updated to include more detailed information and improved illustrations.

In Summary

It is hoped that the APGG2 will continue to increase awareness of glaucoma and update glaucoma knowledge, thereby reducing visual disability in the region. The guidelines are intended to provide a rational basis for appropriate individual glaucoma management in a cost-effective manner in a mutually supportive community. APGG2 is not intended to be a text book, but has been designed to complement and facilitate access to information. The focus is a patient-oriented approach, with which to guide people with glaucoma through appropriate assessment and care.

The Asia Pacific Glaucoma Guidelines Second Edition are available from the SEAGIG website at: **www.seagig.org**

The guidelines are also available in CD-ROM format, which contains the abstracts of all the references cited in the guidelines. For further information, please e-mail to: **editor@seagig.org**

Acknowledgements

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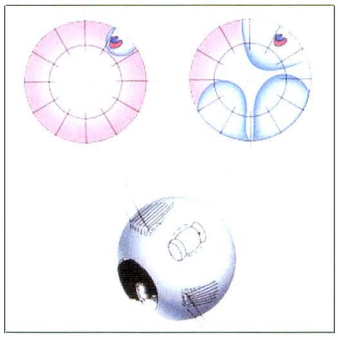

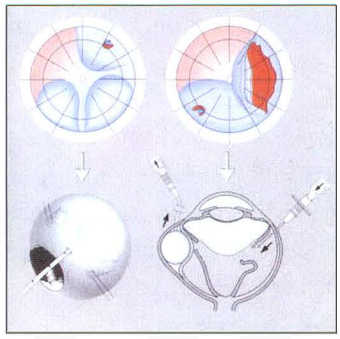

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The Joint Meeting of the Asia-Pacific Academy of Ophthalmology and the American Academy of Ophthalmology (APAO-AAO 2009) will be held in Bali, Indonesia, on 16-19 May 2009. The APAO-AAO 2009 is the most important congress of the Asia-Pacific region, with more than 5000 delegates anticipated. More than 500 international speakers have agreed to join the scientific program and 44 international, supranational, and national organisations have given their support for the Congress.

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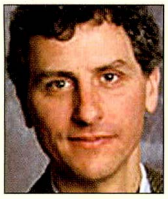
Mechanisms of Angle Closure



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Angle Closure Terminology

People who are primary angle closure suspects do not have a disease. Gonioscopic examination suggests an 'appearance' of an abnormality, in that the posterior trabecular meshwork is not visible, but there is no evidence of optic disc or visual field damage (Table 1).

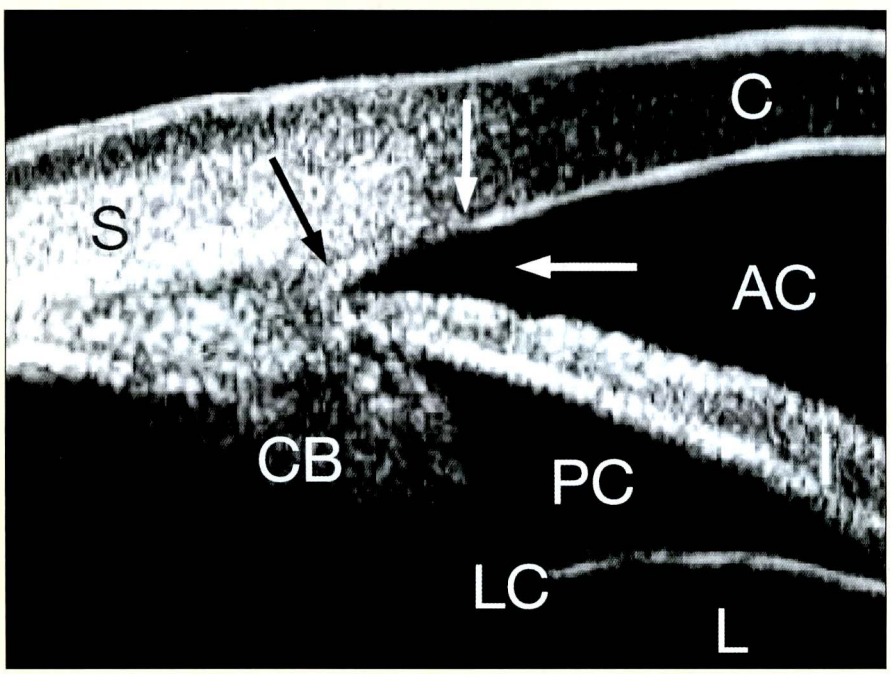
Primary angle closure (PAC) is of greater concern because of an abnormality within the eye that was likely to have been caused by angle closure. Evidence of damage is shown by the presence of peripheral anterior synechiae (PAS) or elevated intraocular pressure (IOP). The term glaucoma (or primary angle closure glaucoma [PACG]) is reserved for eyes with characteristic optic neuropathy with optic disc and/or visual field changes.

Acute angle closure has a characteristic appearance of sudden IOP elevation, and requires urgent treatment. The condition can cause severe damage, and 1 in 10 people who experience an acute angle closure attack will become blind in the affected eye within 10 years.

Table 1. Definitions of angle closure.

Primary angle closure suspect	No evidence of disease Unable to view posterior trabecular meshwork Intraocular pressure <95th percentile for the population No evidence of optic disc or visual field damage
Primary angle closure	Iridotrabecular contact Evidence of secondary effect No optic disc or visual field damage
Primary angle closure glaucoma	Iridotrabecular contact Optic disc or visual field damage as defined for open angle glaucoma
Acute angle closure	Sudden elevation in intraocular pressure associated with a closed angle Classic signs and symptoms

Figure 1. Angle anatomy viewed by ultrasound biomicroscopy.
Abbreviations: AC = anterior chamber; C = cornea; CB = ciliary body; I = iris; L = lens; LC = lens capsule; PC = posterior chamber; S = sclera.



Anatomical Mechanisms

The mechanisms of angle closure are anatomical, and relate to both static and dynamic structural findings. Gonioscopy is the current reference standard for examining the eye, as it provides direct visualisation of the angle structures, as well as PAS. Using a narrow beam, the corneal wedge will guide the examiner in establishing the position of the angle structures and the presence of angle closure.

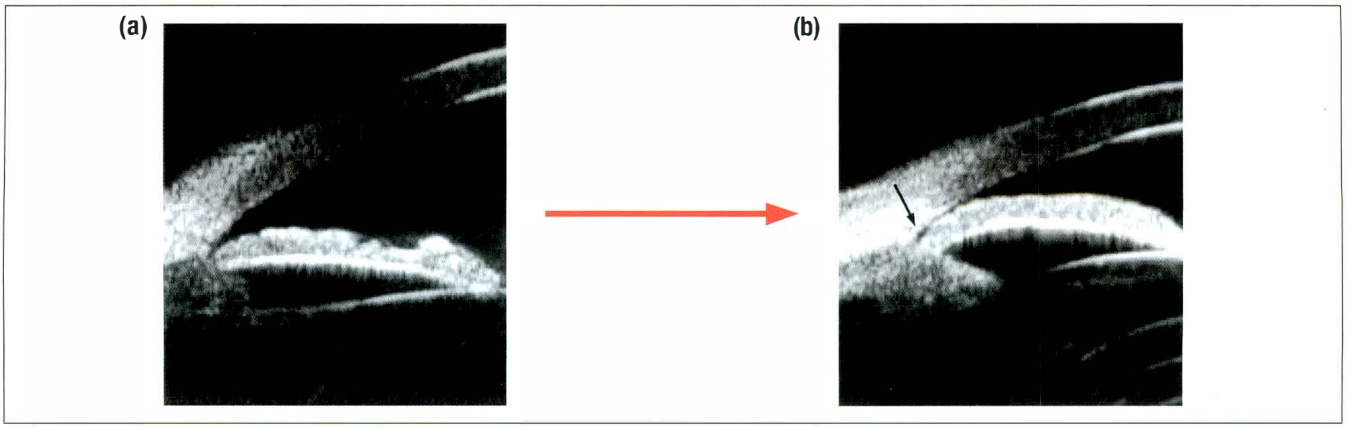
Ultrasound biomicroscopy (UBM) enables the anatomy to be viewed in detail. Figure 1 shows the structures of the angle visualised by UBM. Figures 2a and b show open and closed angles, respectively.

UBM enables clear visualisation of the iris, which is important as the iris anatomy can affect the angle structure. Iris insertion varies considerably, and these anatomical differences can affect the prognosis. Variable iris configuration in the form of plateau iris or pupil block can affect the angle anatomy. An extra roll of tissue in the peripheral iris (iris roll) can cause occlusion of the angle. In addition, the ciliary body position varies considerably and can block the angle.

Light-dark changes when performing UBM can affect visualisation of the angle structures. A 1-mm bright beam is the preferred light source.

Pupil block is important in angle closure. Gonioscopy shows that the median angle width increased by 2 grades following laser peripheral iridotomy (LPI) in Mongolian eyes with angle closure. While similar results have been shown in China, not all closed angles open after LPI.[1] Risk factors for angles

Figure 2. Ultrasound biomicroscopy showing (a) an open angle; and (b) a closed angle.



remaining closed include narrow angles, anterior iris insertion, thick iris, and short distance from the scleral spur to the ciliary body.

Plateau Iris Configuration

Plateau iris configuration is a term that has not been clearly defined using standardised approaches. In a recent UBM study of plateau iris, it was defined as:

- angle closure in the presence of anteriorly rotated ciliary processes supporting the peripheral iris against the trabecular meshwork
- narrow or absent ciliary sulcus
- iris root angulating forward and then centrally with a flat iris contour
- at least 2 quadrants had to fulfil the criteria for an eye to be defined as plateau iris.

A recent UBM study of Chinese eyes in Singapore found that 54 of 167 eyes (32.9%) had plateau iris before LPI.[2] After LPI, 42 of 54 eyes still had plateau iris, and 11 eyes without plateau iris before LPI had this configuration. In the latter group, bowing of the iris had concealed the plateau, which became evident after treatment.

The lens plays a major role in plateau iris configuration. Several studies have demonstrated posterior movement of the ciliary body following lens extraction, which alters the plateau configuration.[3,4] Performing cataract extraction instead of iridectomy for acute angle closure results in a reduced need for IOP-lowering treatments after surgery.[5] A recent trial of cataract extraction performed during an acute angle closure attack has shown that this approach improves IOP control over time.[6]

Although there is no evidence that cataract extraction is effective for PACG, observational studies have shown an IOP-lowering effect of lens extraction.[7] This may be a useful approach for PACG, but randomised studies are required.

In Summary

Several mechanisms are involved in ACG, including pupil block, ciliary body, and lens. LPI is the recommended treatment, even in the presence of plateau iris, although some angles may remain closed after treatment. Cataract extraction opens the angle and can lower IOP, but the risk-benefit profile needs to be considered.

Ultrasound Biomicroscopy-defined Plateau Iris

- Angle closure in the presence of anteriorly rotated ciliary processes supporting the peripheral iris against the trabecular meshwork
- Narrow or absent ciliary sulcus
- Iris root angulating forward and then centrally with a flat iris contour
- At least 2 quadrants had to fulfil the criteria for an eye to be defined as plateau iris

Kumar RS, Baskaran M, Chew PT, et al. Prevalence of plateau iris in primary angle closure suspects an ultrasound biomicroscopy study. Ophthalmology. 2008;115:430-4.

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Medical Treatment for Angle Closure Glaucoma

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There are 3 basic principles of management of angle closure glaucoma (ACG): modification of the angle configuration, intraocular pressure (IOP) control, and monitoring and detection of changes to the optic disc and visual field. Laser peripheral iridotomy (LPI), iridoplasty, topical pilocarpine, or lens removal are options for modifying the angle configuration. However, LPI is not always successful, with up to 60% of patients having increased IOP at long-term follow-up. Options for IOP control after LPI include medical therapy, laser treatment, or filtering surgery.

The steps for the management of ACG are as follows:

- documentation of the angle structures and optic nerve head damage
- identification of angle closure mechanism(s)
- treatment with medication and LPI
- assessment after LPI for further treatment
- monitoring of IOP, optic disc, and visual field, and appropriate treatment adjustment.

According to the Asia Pacific Glaucoma Guidelines, medical treatment is effective for long-term treatment of ACG after LPI and has an acceptable therapeutic index.[1] Although several medications are available for treatment of ACG, including prostaglandin analogues (PGAs), β-blockers, and α-agonists, the PGAs are the most effective.

Chronic angle closure glaucoma (CACG) is the most common form of angle closure. Filtering surgery is usually the next step after LPI, as iridoplasty has no proven efficacy for CAGC. However, the outcomes are variable. Therefore, medical treatment for control of IOP is increasingly important.

Medication Efficacy

As well as knowing which medications are most effective for lowering IOP, it is important to know the expected percentage IOP reduction when aiming for a specific target pressure.

The Efficacy of Xalatan in Chronic Angle Closure Glaucoma Therapy (EXACT) study was the first multicentre randomised controlled trial to compare the IOP-lowering effect of latanoprost and timolol in Asian patients with CACG.[2] 275 patients with IOP ≥21 mm Hg were enrolled from 7 Asian countries to receive either latanoprost or timolol. After 12 weeks, the mean absolute IOP reduction with latanoprost was 8.2 mm Hg compared with 5.2 mm Hg for timolol ($p < 0.001$) [Figure 1], a decrease of approximately 30% for latanoprost and 20% for timolol (Figure 2). The safety profile was acceptable for both medications.

Figure 1. Mean absolute intraocular pressure reduction with latanoprost or timolol.
* $p < 0.001$.

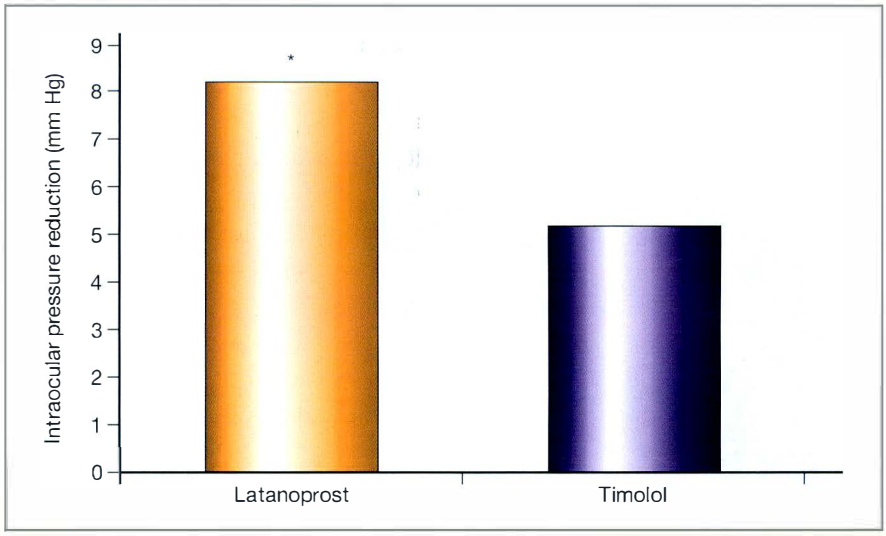


Figure 2. Mean percent intraocular pressure reduction with latanoprost or timolol.

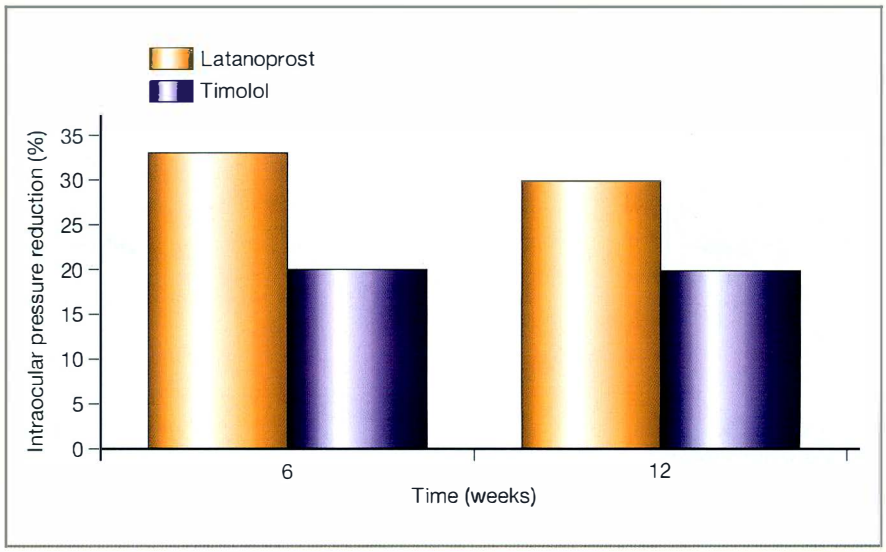
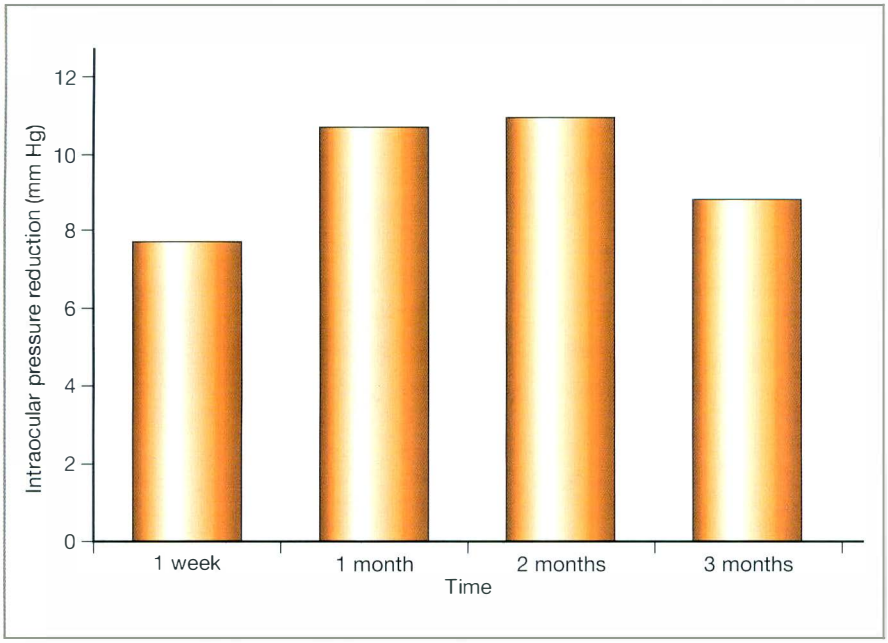


Figure 3. Intraocular pressure reduction with latanoprost in eyes with peripheral anterior synechiae.



The conclusions drawn from this study were that latanoprost results in significantly greater IOP reduction than timolol for patients with CACG. More patients reached lower IOP levels after 12 weeks of treatment with latanoprost than with timolol. Both medications were well tolerated. Latanoprost is a good therapeutic option for CACG. Based on the risk categories, latanoprost may be a suitable first-line medication for certain patients.

Further analysis of the EXACT study population to investigate the configuration of the drainage angle, IOP, and cupping in CACG found that the extent of peripheral anterior synechiae (PAS) and narrower drainage angle width were associated with higher untreated IOP and larger vertical cup-disc ratio.[3] This analysis suggests a high correlation between degree of PAS and magnitude of IOP increase.

A subgroup analysis to examine whether there was a correlation between the degree of angle closure and the magnitude of IOP-lowering from latanoprost found that the IOP-lowering efficacy of latanoprost was unaffected by the degree of angle closure or extent of PAS.[4]

Kook et al studied 14 eyes with 360° PAS treated with latanoprost.[5] All eyes responded well to latanoprost, with >30% IOP reduction achieved (Figure 3). Seven eyes had undergone LPI >6 months previously, all of which exhibited similar IOP reduction, suggesting that previous LPI does not affect the IOP-lowering efficacy of latanoprost.

Studies of other PGAs have shown similar IOP-lowering efficacy in comparison to timolol for CACG.[6,7] However, there may be slight differences in ocular hypotensive efficacy, response rate, and safety profile among different PGAs.

Mechanism of Action

CACG is caused by mechanical closure of the trabecular meshwork, resulting in less available open trabecular meshwork and impaired 'conventional' outflow. The mechanism of action of PGAs is not dependent on trabecular outflow, as these medications also act on uveoscleral outflow. PGAs facilitate outflow through the iris and ciliary body and need only small access to the uveoscleral channel to achieve efficacy. This may explain why there is no correlation between the degree of PAS and efficacy of PGAs.

In Summary

Medical treatment is usually required after successful LPI for CACG. PGAs offer greater IOP reduction than β-blockers or α_2-agonists. When treating patients there are several factors to consider: efficacy, safety profile, adherence, and persistence. These core treatment values must be applied to each individual patient when selecting treatment.

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From the Pfizer Angle-Closure Symposium *held at the 5th Congress of the South East Asia Glaucoma Interest Group and 6th Meeting of the Asian Angle-Closure Glaucoma Club, Seoul, Korea, 27 September 2008.*

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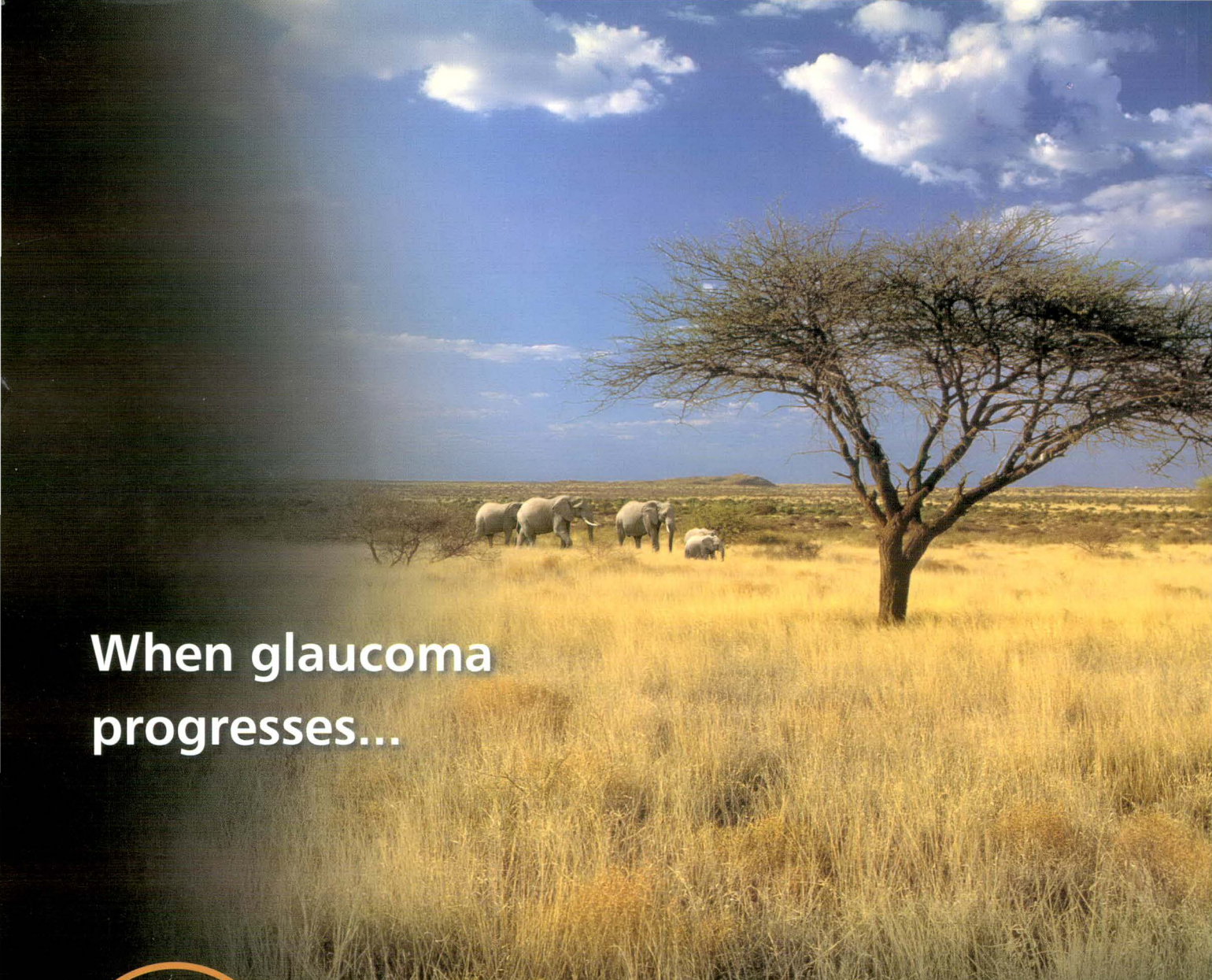

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In the 6-month registration trials, the most frequent adverse events were eye irritation, including stinging, burning, and itching (12.0%); eye hyperemia (7.4%); corneal disorders (3.0%); conjunctivitis (3.0%); blepharitis (2.5%); eye pain (2.3%); headache (2.3%); and skin rash (1.3%)'.

Summary of Prescribing Information

Composition: Bottles containing 2.5 ml ophthalmic solution, 1 ml contains 50 mcg of latanoprost and 6.8 mg of timolol maleate equivalent to 5 mg timolol. **Indications:** Reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma and ocular hypertension insufficiently responsive to topical beta blockers and PG analogues **Contraindications:** Reactive airway disease including bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease, sinus bradycardia, second or third-degree atrioventricular block, overt cardiac failure, or cardiogenic shock, known hypersensitivity to latanoprost, timolol maleate, or any other component of the product. **Adverse Reactions:** Adverse events observed in 1% of the patients treated with Xalacom during clinical development were: abnormal vision, blepharitis, cataract, conjunctival disorder, conjunctivitis, corneal disorder, errors of refraction, eye hyperemia, eye irritation, eye pain, increased iris pigmentation, keratitis, photophobia, and vision field defect. Other systemic reactions include infection, sinusitis, and upper respiratory tract infection,diabetes mellitus, hypercholesterolemia, depression, headache, hypertension, hypertrichosis, rash, and skin disorder and arthritis **Warnings and Precautions:** Latanoprost: increased brown pigmentation of iris, reversible eye lid skin darkening. May gradually change eyelashes and vellus hair in the treated eye, heterochromia, and macular edema, including cystoid macular edema. Limited experience in the treatment of inflammatory neovascular or congenital glaucoma. No adequate and well-controlled studies in pregnant women, use with caution in nursing women. Timolol: Monitor patients with severe heart disease for signs of cardiac failure. Aggravation of Prinzmetal's angina, aggravation of peripheral and central circulatory disorders, hypotension, fatal cardiac failure, severe respiratory reactions such as fatal bronchospasm in patients with asthma and bradycardia may occur. Consider gradual withdrawl prior to major surgery. Used with caution in patients with spontaneous hypoglycemia or diabetes, may mask certain signs and symptoms of hyperthyroidism. Patients with h/o atopy/ severe anaphylactic reaction to allergens may be more reactive to repeated challenge with such allergens. May increase muscle weakness in patients with myasthenia gravis/ myasthenic symptoms; choroidal detachment after filtration procedures. Patients should not drive or use machines while on Xalacom. **Dosage:** One drop in the affected eye(s) once daily. Dose should not exceed once daily. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart. Safety and effectiveness not established in children.

Please refer to the SmPC before prescribing Xalacom® (Latanoprost and Timolol maleate)

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