Effect of Trabeculectomy on Lens Opacities in an East Asian Population

Rahat Husain, MRCOphth; Tin Aung, FRCS(Ed), FRCOphth; Gus Gazzard, FRCOphth; Paul J. Foster, PhD, FRCS(Edin); Joe G. Devereux, FRCOphth; Paul T. K. Chew, FRCOphth, MMed(Sing); Francis T. S. Oen, FRCOphth, MMed(Sing); Peng T. Khaw, PhD, FRCP, FRCOphth; Steve K. L. Seah, FRCS(Glasg), FRCOphth, MMed(Sing)

Objective: To examine the progression of lens opacity in Asian people after trabeculectomy and determine associated risk factors.

Methods: This was an observational case series of 243 people aged 36 to 82 years. Trabeculectomy was performed on 1 eye of each subject. Lens opacity was measured yearly using the Lens Opacification Classification System III. The main outcome measure was worsening of lens opacity defined as an increase of 2 or more Lens Opacification Classification System III units in any of the 3 lens regions, nuclear, cortical, and posterior subcapsular. Risk of progression was evaluated using logistic regression models.

Results: Data for 177 people were analyzed. One hundred seventeen (66%) of 177 subjects showed progression in opacity in any lens region at 3 years. Seventy-seven (66%) of 117 of those who progressed did so during the first year. Of these, 63 (82%) of 77 had lens opacity in the posterior subcapsular region. Factors associated with progression of posterior-subcapsular lens opacity at 1 year were diabetes (odds ratio, 2.4; 95% confidence interval, 1.0-5.4), use of antiglaucoma medication, dosage of topical steroid postoperatively, and being operated on by a trainee surgeon (odds ratio, 2.3; 95% confidence interval, 1.0-5.2).

Conclusions: Trabeculectomy is associated with progression of lens opacity predominantly in the posterior subcapsular region. Modification of risk factors such as postoperative steroid use may delay progression.

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Author Affiliations: Institute of Ophthalmology, University College, London, England (Drs Husain, Gazzard, Foster, Devereux, and Khaw); Singapore National Eye Centre (Drs Husain, Aung, Gazzard, Devereux, Chew, Oen, and Seah); Glaucoma Research Unit, Moorfields Eye Hospital, London (Drs Husain, Gazzard, Foster, Devereux, and Khaw); and Singapore Eye Research Institute (Drs Husain, Aung, Gazzard, and Seah).

TRABECULECTOMY IS THE most common surgical intervention to lower intraocular pressure (IOP) in the management of glaucoma. It achieves lower IOPs than medical or laser treatments alone[1-5] but is associated with more sight-threatening complications.[6,7] There is accumulating evidence that trabeculectomy hastens the development of cataract.[5,8-11] A recent systematic review found strong evidence that glaucoma surgery increases the risk of development and progression of cataract.[12] This compromises the visual outcomes of otherwise successful trabeculectomy surgery and limits the benefits of reduced IOP.

Previous studies analyzing the relationship between trabeculectomy and cataractogenesis have been mainly retrospective or involved fewer than 50 patients. Most have been performed on predominantly white or black populations, yet approximately half of the world's estimated 67 million glaucoma sufferers are of East Asian origin.[13] Most of the glaucoma sufferers of Asia reside in developing countries with few ophthalmologists. Medical treatment is often unavailable or unaffordable. Primary trabeculectomy in the manner of cataract "eye camps" has thus been proposed for some patients.[14] The frequent development of cataract could severely limit the utility of such a scheme.

In the context of limited data on the relationship between glaucoma surgery and cataract, the purpose of this study was to examine prospectively the changes in lens opacity in the first 3 years after trabeculectomy in a large cohort of Asian people and to identify the risk factors associated with such changes.

METHODS

Subjects for this analysis were enrolled in a prospective, randomized, placebo-controlled trial of the effect of 5-fluorouracil (5-FU) augmented trabeculectomy. Written informed consent was provided by all subjects, and the study was granted ethical approval by the ethical review committee of Singapore National Eye Centre. We observed the tenets of the Declaration of Helsinki.

Subjects were recruited from 3 hospitals in Singapore. One inclusion criterion was an IOP greater than 21 mm Hg on at least 1 visit before trabeculectomy. The subject also had to have the ability to complete the Humphrey 24-2 visual field test (Humphrey Field Analyzer Model 750; Zeiss Humphrey Systems, Dublin, Calif) with fewer than 20% false positives, 33% false negatives, and 20% fixation losses and the presence of 2 visual field testing points more than 5 dB less than normal or 1 testing point more than 10 dB less than age-corrected normal. The final inclusion criterion was the presence of an area of optic disc rim loss to less than one tenth of the disc diameter or a disc that, in the view of the patient's fellowship-trained glaucoma specialist, showed glaucomatous change. The exclusion criteria for the study were anterior segment neovascularization; aphakia; previous glaucoma filtration surgery; uveitis; any previous intraocular surgery; age younger than 30 years; any disease causing visual field loss or likely to cause visual field loss over the next 3 years (eg, diabetic retinopathy, stroke, etc); pregnancy; previous conjunctival or squint surgery; and previous chronic use of systemic or topical steroids.

Baseline data included past medical and ophthalmic history, medication usage, and ocular examination. Only subjects with primary open angle glaucoma, pseudoexfoliation glaucoma, pigmentary glaucoma, or primary angle-closure glaucoma were recruited. Glaucoma was defined as glaucomatous optic neuropathy in the opinion of a fellowship-trained glaucoma specialist, together with an IOP greater than 21 mm Hg on at least 1 occasion and reproducible visual field defect (using the 24-2 test pattern) consisting of either 2 points reduced by more than 5 dB or 1 point reduced more than 10 dB below the age-specific threshold with no alternative explanation. Primary angle-closure glaucoma was diagnosed if glaucomatous optic neuropathy was present and the posterior trabecular meshwork was not visible in 270° or more with gonioscopy (without indentation) with or without peripheral anterior synechiae.

Cataract was graded at the slitlamp by ophthalmologists with subjects' pupils fully dilated (tropicamide 0.5%; Alcon-Couvreur, Puurs, Belgium) using Lens Opacity Classification System III[15] (LOCS III) standard color photographs. A grade of lens opacity was applied to each of the 3 regions of the lens, namely nuclear (NO), cortical (CO), and posterior subcapsular (PSC). The grading was recorded to the nearest integer from 0 to 6 (0-7 in the case of NO). For the NO region, the score was taken as the average of the 2 readings of the nuclear opalescence and nuclear color grade. Lens grading was carried out at baseline and then yearly after surgery.

Surgical technique was standardized as follows. A trabeculectomy was performed in all cases with a limbus-based flap at the 12-o'clock position. A precut Weck Cell sponge was placed under the conjunctival flap soaked in either 50 mg/mL 5-FU (David Bull Laboratories Ltd, Warwick, England) or saline placebo before the scleral flap was dissected. Scleral flap closure was with 10-0 nylon sutures. The type of suture material used for conjunctival flap closure was at the surgeon's discretion as were postoperative antibiotic injections.

Topical prednisolone acetate 1% was used at least 4 times a day for a minimum of 3 months in all cases and topical chloramphenicol 0.5% 4 times per day for 4 weeks unless clinically indicated otherwise. A higher dosage of topical steroids could be used if judged necessary. Postoperative physical maneuvers such as bleb massage, suture lysis, and bleb needling were all permitted. Subconjunctival injections of 5-FU constituted trial failure and were therefore used only if regarded as clinically indicated.

OUTCOMES

The main outcome measure was progression of lens opacity in any of the 3 lens regions, NO, CO, or PSC, by 2 or more LOCS III units within 3 years after trabeculectomy. A similar definition of progression has been used previously.[16] Subjects who underwent cataract surgery were excluded from the analysis because the indication for cataract extraction was based on patient and physician choice and not necessarily on objective criteria.

DESCRIPTION OF VARIABLES

Age was age at time of entry to the study. Diabetes and hypertension were defined by self-reported status plus either dietary (for diabetes) or pharmacological therapy. Intraoperative complications included a flat anterior chamber and anterior chamber hemorrhage. A trainee surgeon was a registrar or fellow not registered as an independent practitioner. Iridocorneal touch referred to this occurring at any time during the first year after surgery. The amount of topical steroid was the total number of prednisolone acetate 1% drops instilled into the eye during the first year. Hypotony (IOP $\leq$5 mm Hg) referred to any episode on 2 consecutive visits at any time in the first 3 months. Drop-months referred to the combined total number of months a subject was receiving each antiglaucoma medication before trabeculectomy.

STATISTICS

Multivariate analysis was performed using logistic regression to determine risk factors. The null model contained the following variables, chosen for biological plausibility and known risk factors from previous studies: age, total number of steroid drops instilled from postsurgical day 1 to year 1 visit, baseline LOCS score for each lens region, drop-months, sex, ethnicity, diabetes, hypertension, glaucoma diagnosis, intraoperative complications, grade of surgeon, and postoperative hypotony. For the continuous variables (age, LOCS scores, drop-months, and number of steroid drops), the odds ratio refers to the odds of reaching outcome when there is 1-unit increase. For categorical variables, the odds ratio refers to the odds of reaching an outcome compared with the control for that variable. The results were considered significant at $P \leq .05$. A proprietary statistical software package (Statistical Product and Service Solutions version 11.5; SPSS Inc, Chicago, Ill) was used to analyze the data.

RESULTS

Of the 243 subjects enrolled in the study, 2 required a second operation due to uncontrolled IOP before any cataract outcome was reached and they were excluded. A further 7 subjects died and 12 were lost to follow-up. Ten subjects had no LOCS score recorded for either the baseline or year 1 visits because of poor visibility of the lens as a result of small pupils. Over the 3 years, a further 35 subjects were excluded because they underwent cataract extraction before prior documentation of progression. Patient demographics and characteristics for the remaining 177 subjects are listed in **Table 1**. **Figure 1** illustrates the numbers of subjects included and excluded at enrollment and during follow-up.

Mean ± SD baseline LOCS score for the 3 lens regions for these subjects were as follows: NO, 3.4 ± 0.8; CO, 0.7 ± 1.0; and PSC, 0.2 ± 0.6. The maximum baseline LOCS score for the NO, CO, and PSC regions were 5, 4, and 4,

Table 1. Demographics and Ocular Characteristics of Subjects Included in This Study

Factor	Value (N = 177)
Demographic	
Age, mean ± SD, y (range, 36-82 y)	60.1 ± 10.2
Sex, No. (%)	
Male	120 (68.0)
Female	57 (32.0)
Ethnicity, No. (%)	
Chinese	139 (77.2)
Malay, Indian, or other	38 (22.8)
Diabetes, No. (%)	41 (23.9)
Systemic hypertension, No. (%)	57 (32.2)
Ocular Characteristic	
Diagnosis, No. (%)	
Open angle glaucoma	102 (58.4)
Angle-closure glaucoma	75 (41.6)
Intraoperative complications	14 (8.6)
Grade of surgeon operating, No. (%)	
Specialist	128 (73.6)
Trainee surgeon	49 (26.4)
Hypotony, No. (%)	36 (20.3)
Iridocorneal touch, No. (%)	31 (16.8)
Intraoperative 5-FU, No. (%)	91 (51.4)
Vertical cup-disc ratio, mean ± SD	0.77 ± 0.18
Visual field mean deviation, mean ± SD, dB	−16.0 ± 9.3
Visual field pattern standard deviation, mean ± SD, dB	7.5 ± 3.6
Presurgical intraocular pressure, mean ± SD, mm Hg	22.6 ± 6.1
Baseline LOCS III score, mean ± SD	
Nuclear region (median, 3)	3.2 ± 0.8
Cortical region (median, 0)	0.6 ± 1.0
Posterior subcapsular region (median, 0)	0.2 ± 0.5
Steroid drops over the first year, mean ± SD, No.	865 ± 445
Time on antiglaucoma medications before trabeculectomy, mean ± SD, drop-months	29.3 ± 34.0

Abbreviations: 5-FU, 5-fluorouracil; LOCS, Lens Opacification Classification System.

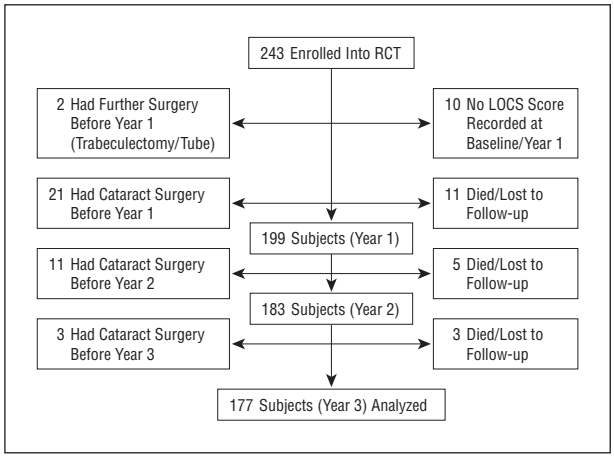

Figure 1. Patient flowchart from enrollment into randomized controlled trial (RCT) to subjects analyzed at year 3. LOCS indicates Lens Opacification Classification System.

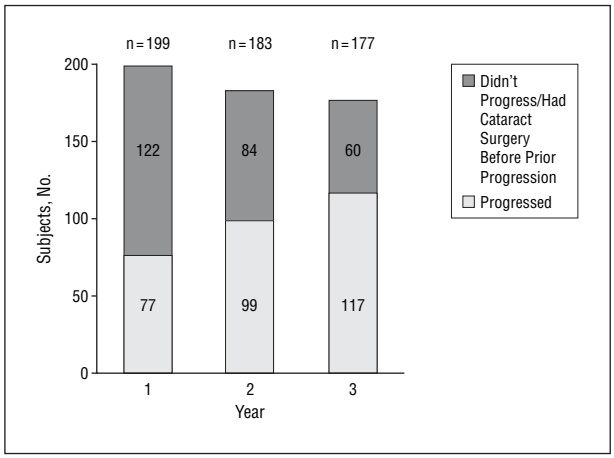

Figure 2. Number of subjects who progressed in any lens region over 3 years.

respectively. Of the 177 subjects included in this analysis, 117 (66%) had worsening of lens opacity in any or all regions by year 3. The cumulative incidence of progression, including rates of cataract surgery, over the 3 years is shown in **Figure 2**. Incidence of progression for each year by lens region is shown in **Figure 3**. Seventy-seven (66%) of 117 of those who progressed were during the first year, and of those, 63 (82%) of 77 were in the PSC region. For the 77 subjects who progressed in the first year, 46 were in the PSC region alone, 5 in the NO region alone, and 9 in the CO region alone. Only 2 subjects progressed in all 3 lens regions (see **Figure 4**).

Because of the small number of subjects who showed lens opacity progression in the NO and CO lens regions and because the majority of progression took place during the first year, risk factor analysis was carried out only for progression of PSC at 1 year. One hundred ninety-nine subjects reached 1-year follow-up, and progression in the PSC region occurred in 63 subjects (32%). We found that in a logistic regression model, the following were significantly associated with worsening of the PSC LOCS score at 1 year: diabetes, non-Chinese race, trainee surgeon, lower level of PSC at baseline, total amount of steroid drops prescribed over the first year, and number of months receiving antiglaucoma drops before surgery (drop-months). The results are summarized in **Table 2**.

The average ± SD age for non-Chinese subjects was 63.7 ± 9.9 years compared with 59.9 ± 10.2 years for Chinese ($P = .03$, unpaired t test). Non-Chinese subjects received more steroids drops on average than the Chinese subjects (1016 ± 547 vs 810 ± 405 drops, respectively; $P = .007$). Including an interaction term for ethnicity and the total number of steroids drops in the multivariate model suggested that race was not a significant independent risk factor ($P = .21$).

After including postoperative hypotony and intraoperative complications with the relevant interaction terms in the multivariate model, having a trainee surgeon was still significantly associated with outcome. Furthermore, there was no significant difference between the mean age, number of steroid drops, and months receiving preoperative drops used between those subjects operated on by a consultant or a trainee surgeon ($P > .05$).

Topical steroids were used for more than 3 months in 103 subjects of the 199 who reached 1-year follow-up (52%). Using a duration of steroid use of more

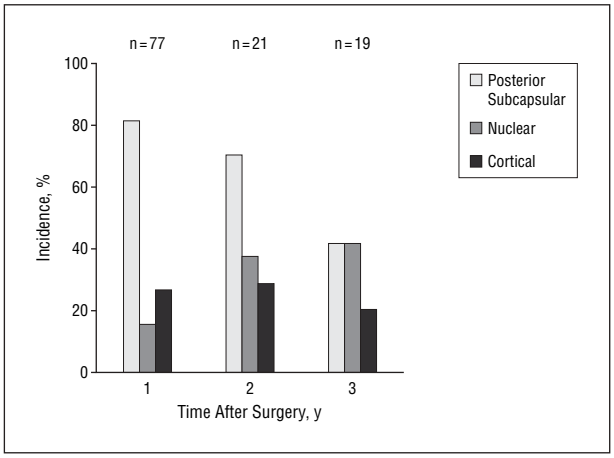

Figure 3. Incidence of progression for each year by lens region.

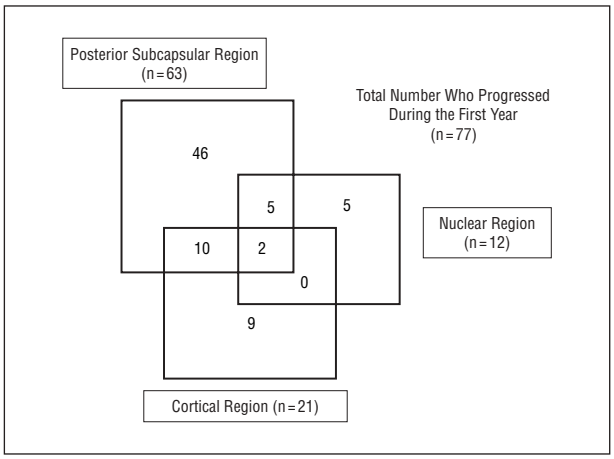

Figure 4. Venn diagram of subjects that progressed at 1 year posttrabeculectomy by lens region.

or less than 3 months as a dichotomous variable, we found duration more than 3 months to be significantly associated with worsening of PSC lens opacity in the multivariate analysis ($P=.01$; OR, 2.7). Using the quantity of steroid drops applied in the first 6 weeks in the multivariate model instead of 1 year, we found that steroids were not retained in the final model ($P=.20$).

There were 124 (62%) of 199 subjects taking 4% pilocarpine, 185 (93%) of 199 were taking 0.5% timolol maleate, and 42 (21%) of 199 were taking other topical antiglaucoma medications before enrollment into the study. If we included preoperative use of timolol or preoperative use of pilocarpine in the multivariate model instead of number of months receiving any medication, use of pilocarpine was significantly associated with worsening of PSC lens opacity ($P=.04$; OR, 2.3; 95% CI, 1.1-5.2) and timolol was not ($P=.81$). Duration of preoperative pilocarpine use (in months) was also significantly associated with worsening of PSC if duration was substituted into the model ($P=.008$; OR, 1.03; 95% CI, 1.01-1.06).

COMMENT

Our results show that almost two thirds of subjects had worsening of lens opacity in any region of the lens within the first 3 years after trabeculectomy. Of these, 66% were in the first year with the PSC region implicated in 82% of cases. By analyzing risk factors in a multivariate model, we found that having diabetes, being operated on by a trainee surgeon, receiving antiglaucoma medications for longer periods preoperatively, and receiving more postoperative steroid drops all contributed significantly and independently to worsening of PSC lens opacity in Asian subjects at 1 year.

Table 2. Multiple Logistic Regression Model Identifying Risk Factors for Progression of Posterior Subcapsular Lens Opacity at 1 Year Posttrabeculectomy

Variable	*P* Value	OR (95% CI)
Female sex	.12	1.9 (0.9-4.1)
Non-Chinese race*	.02	2.7 (1.1-6.4)
Diabetes*	.04	2.4 (1.0-5.4)
Hypertension	.24	1.6 (0.7-3.6)
Primary angle-closure glaucoma	.45	1.4 (0.6-3.0)
Intraoperative 5-fluorouracil	.75	1.1 (0.5-2.3)
Intraoperative complication	.15	0.3 (0.9-1.5)
Trainee surgeon*	.04	2.3 (1.0-5.2)
Hypotony	.55	1.4 (0.5-3.8)
Iridocorneal touch	.41	1.6 (0.6-4.4)
Nuclear region LOCS III score at baseline	.43	1.3 (0.7-2.3)
Cortical region LOCS III score at baseline	.98	1.0 (0.7-1.4)
Posterior subcapsular region LOCS III score at baseline*	.001	0.2 (0.1-0.5)
Age at study entry	.19	1.03 (0.98-1.09)
Number of postoperative steroid drops*	<.001	1.002 (1.001-1.003)
Months on antiglaucoma drops before operation*	.04	1.01 (1.00-1.02)

Abbreviations: CI, confidence interval; LOCS, Lens Opacification System; OR, odds ratio.
*$P \leq .05$ is counted as significant.

Studies of risk factors for cataract development after trabeculectomy are summarized in **Table 3**. In general, our results agreed with the findings of other studies, such as the association with diabetes with PSC lens opacity development after trabeculectomy. In addition, we identified some associations that had not been reported before. A recent study conducted by the Advanced Glaucoma Intervention Study investigators identified a number of risk factors associated with increased rate of cataract development after trabeculectomy.[11] Specifically, they found that subjects undergoing trabeculectomy developed cataract earlier than those treated initially with argon laser trabeculoplasty. Within this surgically treated group, peroperative complications, older age, diabetes, female sex, and black race were all significantly associated with earlier development of cataract in 1 or more lens regions. The criterion used to assess cataract was based on visual acuity which, by the authors' own admission, is less objective than other clinical grading systems such as the LOCS III. There were also some aspects not assessed in the analyses such as amount of postoperative topical steroid use.

We found that being operated on by a trainee surgeon was associated with worsening of PSC lens opacity. This link has not been reported before, to our knowl-

edge. The reason why surgery by a trainee surgeon should result in the earlier development of cataract is not clear. It may be that other, more subtle factors such as longer surgical time, excessive iris manipulation, or fluctuations in anterior chamber depth may occur more often with trainee surgeons. The positive role of aqueous transforming growth factor β in cataract formation may be relevant in this scenario.[20,21] McAvoy et al[20] found that incubating lenses with transforming growth factor β resulted in an increase in lens opacity predominantly in the PSC region. Trabeculectomy performed by a trainee surgeon may result in more tissue damage, causing a larger breakdown of the blood aqueous barrier. As a consequence of this, there may be increased bioavailability of cytokines in the anterior chamber, including transforming growth factor β, which would then account for the increased rate of progression of PSC lens opacity.

An alternative explanation could be considered. Trainee surgeons in Singapore often identify cases for surgery from government-subsidized clinics whereas senior specialists are more likely to operate on fee-paying patients. Lower socioeconomic status has been associated with PSC lens opacity in a Singaporean cataract prevalence survey.[22] The link between trainee surgeon and greater cataract progression might reflect the lower socioeconomic status of those operated on.

We found that increased use of postoperative steroid drops was significantly associated with worsening of PSC lens opacity and were able to quantify this. Topical steroids are known to increase cataract development, especially in the PSC region.[23] They have also been shown to improve success rates in terms of IOP control posttrabeculectomy.[24] Although there is evidence for a correlation between dosage and duration of oral steroid use and cataract formation,[25] this has not been established for topical steroids. Our results suggest that topical steroid use for the short term may not be cataractogenic, but if used for longer periods it becomes so and then the quantity used becomes significant. Clinicians have tended to give steroid drops intensively initially and then tail off the frequency over 3 months, although there is little evidence that this is the best regimen. It seems likely that a delicate balance exists between too little steroid, resulting in a suboptimal surgical result, and too much steroid, resulting in the earlier formation of cataract.

A possible reason for why increased steroid use was associated with worsening of lens opacity in our study is that eyes with increased inflammation required more steroids, and therefore it may be inflammation itself that is cataractogenic and the amount of steroid received acts only as a surrogate for this. However, the frequency of steroid drops after trabeculectomy is dependent on the appearance of the filtration bleb rather than anterior chamber inflammation, which is usually minimal. Furthermore, steroid use and formation of cataract, particularly in the PSC region, has biological plausibility.

Duration of use of topical antiglaucoma medication was associated with worsening of PSC lens opacity. There are 2 possible explanations for these findings. First, a component of topical medication could be contributing to the worsening of lens opacity. Benzalkonium chloride, the most common preservative used in topical eye medication, is a possible candidate and has been suggested as being cataractogenic previously.[26] The second possibility is that the medications themselves are cataractogenic. Our results suggest that it is more likely that pilocarpine itself may be the cause. Pilocarpine has been associated with cataract formation, although the mechanism is yet to be elucidated.[27-29] Pilocarpine is being used less frequently in Western countries but still has wide usage in East Asia due to the higher prevalence of primary angle-closure glaucoma and also for economic reasons. As newer medications become more accessible and as the economies in these countries improve, pilocarpine use may decrease.

We found a diagnosis of diabetes at study entry to be associated with development of PSC lens opacity, which were also the findings of the Advanced Glaucoma Intervention Study.[11] The prevalence of diabetes in Singapore,[30,31] Taiwan,[32] Hong Kong,[33] and China[34-36] is on the increase, and this has implications for the management of these subjects following trabeculectomy. Cataract not only obscures the view of the posterior pole, making monitoring of diabetic retinopathy problematic, but also cataract extraction in diabetics can worsen preexisting macular edema.

Contrary to expectations, we found that lower grade of PSC lens opacity at baseline was a significant risk factor for progression of PSC lens opacity at 1 year. The majority (83%) of subjects had a baseline PSC LOCS III score of 0 and only 6% had a score of 2 or more. An increase of 2 LOCS III units is clinically easier to detect in a subject with a score of 0 than in a score of 2 or more, and therefore our results may be a reflection of inadequacies of the LOCS III grading system.

This study has some limitations. The grading of lens opacity by the LOCS III grading system is subjective, although most studies have used similar methods. Thirty-five subjects underwent cataract surgery without meeting our criteria for progression. These subjects may have had progression of lens opacity (which prompted the request for cataract surgery) and yet we were unable to include them in our analysis because the location and amount of progression (if any) were not recorded. There

Table 3. Risk Factors for Progression of Lens Opacities After Trabeculectomy From Previous Studies

Risk Factor	Any Cataract Surgery	Regional Lens Opacity		
		Nuclear	Cortical	Posterior Subcapsular
Older age[10,11,17]	X		X	
Black race[11]		X	X	
Diabetes[11]		X		X
High systolic blood pressure[10]		X	X	
Hypotony[17,18]	X			
Intraoperative complications[11]	X			
Anterior chamber inflammation[11]	X			
Flat anterior chamber[11]	X			
Lenticulocorneal touch[18]	X			
Trabeculectomy technique[19]	X			

are a number of variables that we did not include in our analysis but have nonetheless been shown to influence cataract formation, such as smoking, body mass index (calculated as weight in kilograms divided by the square of height in meters), etc. However, the number of subjects in our study limits the number of variables we could consider for the results to remain meaningful.

This study has highlighted a number of risk factors associated with the development of lens opacity in Asian people who have had trabeculectomy. This has a clinical relevance because it appears that avoiding use of pilocarpine for long periods preoperatively and judicious use of postoperative steroid (particularly in regard to duration of use) may delay the onset of cataract. Although this study did not compare the rate of cataract progression after trabeculectomy with a control group, it is evident that trabeculectomy results in a disproportionately greater progression of PSC opacity compared with NO or CO. It is likely that this is due in a large part to the dose and duration of postoperative topical steroid. Further long-term, comparative studies are required to investigate this further as are studies to determine the optimal dose and duration of steroids to ensure surgical success.

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Correspondence: Steve K. L. Seah, FRCS(Glasg), FRCOphth, MMed(Sing), Singapore National Eye Centre, 11 Third Hospital Ave, Singapore 238844 (snecss@pacific.net.sg).
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