Cataract Surgery After Trabeculectomy

The Effect on Trabeculectomy Function

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Objective: To determine whether the timing of cataract surgery after trabeculectomy has an effect on trabeculectomy function in terms of intraocular pressure control.

Methods: This was a cohort study nested within a randomized clinical trial. There were 235 participants with glaucoma who had a single previous trabeculectomy augmented with either intraoperative 5-fluorouracil or placebo. Cataract surgery with intraocular lens implantation was performed on participants judged to have significant lens opacity. Cox regression was performed to evaluate the effect of time between trabeculectomy and cataract surgery on the time to trabeculectomy failure, after adjusting for other relevant risk factors. The main outcome measure was time to failure of trabeculectomy, defined as an intraocular pressure of greater than 21 mm Hg.

Results: Of the 235 participants, 124 (52.7%) underwent subsequent cataract surgery. The median time from trabeculectomy to cataract surgery for these patients was 21.7 months (range, 4.6-81.9 months). The median follow-up period was 60 months (range, 28-84 months) for the cataract surgery group and 48 months (range, 12-84 months) for the non–cataract surgery group. Cox regression showed that the time from trabeculectomy to cataract surgery was significantly associated with time to trabeculectomy failure (hazard ratio, 1.73 [95% CI, 1.05-2.85]; P = .03). The adjusted declining hazard ratios for risk of subsequent trabeculectomy failure when cataract surgery was performed 6 months, 1 year, and 2 years after trabeculectomy were 3.00 (95% CI, 1.11-8.14), 1.73 (95% CI, 1.05-2.85), and 1.32 (95% CI, 1.02-1.69), respectively.

Conclusions: Cataract surgery after trabeculectomy increases the risk of trabeculectomy failure, and this risk is increased if the time between trabeculectomy and cataract surgery is shorter.

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Cataract and glaucoma, both primarily diseases of old age, frequently coexist. The question often arises as to the best management of patients with these conditions in order to preserve or improve sight and, subsequently, quality of life. The options are to perform cataract extraction followed by filtration surgery (ie, trabeculectomy), perform trabeculectomy first followed by cataract extraction, or perform a combined procedure. To decide on the best course of action, it is important to have good quality data on which to base this decision. Analyzing the effect of cataract surgery on eyes that have undergone a previous trabeculectomy will help in deciding the best course of action in patients with glaucoma and cataract.

There are a number of difficulties in trying to resolve this issue. The natural history of a filtration bleb is to fail with time owing to scarring; this would result in increased intraocular pressure (IOP). It is important to differentiate any increased rate of trabeculectomy failure after cataract surgery from that which would occur anyway owing to the natural history of the filtration blebs. Many studies\textsuperscript{1-10} have shown worsening of IOP after cataract surgery compared with a similar time period before surgery, but such analyses do not prove that it is the cataract surgery itself that is the cause of the increased failure rate. In 2002, Friedman et al\textsuperscript{11} conducted an extensive review of the literature to address the question of whether cataract extraction in patients with functioning filtering blebs negatively affects long-term IOP control in patients with glaucoma. Examining publications between the years 1964 and 2000, they found only 5 articles that...
met their criteria for inclusion in the analysis. Friedman et al13 concluded that the data were inconclusive as to whether cataract extraction negatively affects preexisting blebs (evidence grade 1). In our study, we examine the effect of elective cataract extraction (predominantly phacoemulsification) on trabeculectomy function in terms of IOP control in a large cohort of patients with glaucoma who had previously undergone trabeculectomy.

### METHODS

Participants were enrolled in a prospective, randomized placebo-controlled trial of the effect of 5-fluorouracil (5-FU)–augmented trabeculectomy (the Singapore 5-FU Trial).12 We obtained written informed consent from all participants, and our study was granted ethical approval by the institutional review board of the Singapore Eye Research Institute and was conducted in accordance with the tenets of the Declaration of Helsinki.

The study method has been previously described elsewhere13 and is summarized as follows. Participants were recruited from 3 hospitals in Singapore. The inclusion and exclusion criteria are listed in Table 1. Glaucoma was defined as glaucomatous optic neuropathy, in the opinion of a fellowship-trained glaucoma specialist, with an IOP of greater than 21 mm Hg on at least 1 occasion and a reproducible visual field loss over the next 3 years (eg, diabetic retinopathy or cerebrovascular accident) and was the mean of 2 or 3 repeated measurements.

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tr>
<td>IOP &gt;21 mm Hg on at least 1 visit before trabeculectomy</td>
<td>Anterior segment neovascularization</td>
</tr>
<tr>
<td>Ability to complete Humphrey 24-2 visual field test with &lt;20% false positives, &lt;33% false negatives, and &lt;20% fixation losses and the presence of 2 locations &gt;5 dB less than normal or 1 location &gt;10 dB less than age-corrected normal</td>
<td>Aphakia</td>
</tr>
<tr>
<td>The presence of an area of optic disc rim loss to less than one-tenth of disc diameter or a disc that, in the view of the patient’s fellowship-trained glaucoma specialist, shows glaucomatous change</td>
<td>Previous glaucoma filtration surgery</td>
</tr>
<tr>
<td>Uveitis</td>
<td>Any previous intraocular surgery</td>
</tr>
<tr>
<td>Any disease causing visual field loss or likely to cause visual field loss over the next 3 years (eg, diabetic retinopathy or cerebrovascular accident)</td>
<td>&lt;30 years of age</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Previous conjunctival or squint surgery</td>
</tr>
<tr>
<td>Previous conjunctival or squint surgery</td>
<td>Previous long-term use of systemic or topical steroids</td>
</tr>
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</table>

Abbreviation: IOP, intraocular pressure.

### RESULTS

A total of 235 participants with glaucoma had a previous trabeculectomy augmented with either intraopera-
tive 5-FU or placebo. Of these 235 participants, 124 (52.7%) underwent cataract extraction during the follow-up after trabeculectomy (122 by phacoemulsification and 2 by ECCE). Of these 124 participants, 27 (21.7%) experienced trabeculectomy failure before their cataract surgery and, therefore, were included in the non–cataract surgery group for analyses of time to trabeculectomy failure. The median time from trabeculectomy to cataract extraction was 21.7 months (range, 4.6-81.9 months) (Figure). There were 2 participants who had cataract surgery within 6 months after trabeculectomy, 19 participants who had cataract surgery between 6 and 12 months after trabeculectomy, and 76 participants who had cataract surgery more than 12 months after trabeculectomy. The median follow-up period was 60 months (range, 28-84 months) for the cataract surgery group and 48 months (range, 12-84 months) for the non–cataract surgery group.

Two participants had complicated cataract surgery (both had phacoemulsification): one participant had a posterior capsular rupture requiring an anterior vitrectomy, and the other participant had a wound leak and a flat anterior chamber (after the phacoemulsification), which was repaired successfully the next day. One participant was noted to have choroidal effusion after having undergone phacoemulsification; this required no intervention, and the effusion settled within 1 week. All 3 of the above participants were included in the analysis.

The demographic features and ocular characteristics of the 2 groups of participants (those who had cataract surgery and those who did not) are shown in Table 2. There were no significant differences between the groups apart from age (older in the cataract surgery group) and the fact that a greater proportion of female participants, participants with diabetes, and participants with PACG had cataract surgery.

During the follow-up period, 79 patients (33.6%) experienced trabeculectomy failure. The mean time to trabeculectomy failure was 61.4 months (95% CI, 57.2-65.5). Univariate Cox regression with only the time-dependent variable (time from trabeculectomy to cataract surgery) in the model showed that this was associated with time to trabeculectomy failure with a hazard ratio of 1.63 (95% CI, 0.99-2.69; P=.06). The higher the pretrabeculectomy IOP, the more likely that trabeculectomy failure would occur (P =.01). Although those with open-angle glaucoma had a shorter time to failure than those with PACG, when added to the model, this only marginally affected the magnitude of the time-dependent hazard ratio. The effect of age, diabetes status, and trabeculectomy augmentation was not significant (P=.06, .49, and .24, respectively).

Adjusting the analysis for the presence of glaucoma, diabetes, trabeculectomy augmentation, pretrabeculectomy IOP, number of antiglaucoma drops instilled pretrabeculectomy, number of posttrabeculectomy steroid drops, and age made no substantial difference to the estimated influence of time from trabeculectomy to cataract surgery (hazard ratio, 1.73 [95% CI, 1.03-2.85]; P=.03), which shows that cataract surgery after trabeculectomy increased the risk of trabeculectomy failure (Table 3). The closer these 2 surgical procedures were to each other in time, the shorter the time to trabeculecto-
COMMENT

In this large, prospective study investigating the effect of cataract surgery on eyes that underwent a previous trabeculectomy, our results suggest that having cataract surgery after trabeculectomy does increase the risk of trabeculectomy failure and that the earlier that cataract surgery is performed, the greater the risk of failure.

Excessive scarring at the conjunctival-scleral or scleral-flap interface is the main reason for trabeculectomy failure. There are numerous factors that are associated with excessive scarring, such as race, previous use of topical medication, and age. The increased bioavailability of inflammatory factors at the trabeculectomy site would also increase the risk of bleb failure. Cataract surgery is known to result in significant anterior chamber inflammation. A study by Chee et al of 33 patients with cataracts who underwent phacoemulsification or ECCE used laser flare photometry as a quantitative surrogate for blood-aqueous barrier disruption and postoperative inflammation. Chee et al found that phacoemulsification led to increased flare levels postoperatively, with the levels returning to normal after 30 days. Siriwardena et al also used this technique to measure anterior chamber flare and compared the values in 131 patients who underwent trabeculectomy with the values in 148 patients who underwent phacoemulsification. They found significantly higher levels of postoperative inflammation in the phacoemulsification group at all time points up to 3 months. Flare measurements in the phacoemulsification group only returned to preoperative levels by month 6. In contrast, in the trabeculectomy group, flare levels returned to normal after 4 weeks. The authors concluded that the prolonged low-grade inflammation associated with phacoemulsification is likely a product of lens crystallins, the effect of ultrasound, and a high volume of fluid passing through the eye during surgery. This was thought to result in an upregulation of fibrogenic cytokines in the aqueous humor and, hence, an increased risk of bleb failure. We tend to prescribe postoperative steroid drops for 1 month after cataract surgery; the results of Siriwardena et al suggest that we should increase this period in cases of cataract surgery after trabeculectomy, if excessive scarring is to be reduced.

The question then arises as to the optimum timing of cataract surgery after trabeculectomy. To our knowledge, there is no evidence to date regarding the optimal time for cataract surgery to reduce risk of trabeculectomy failure. Chen et al suggested that the optimal time to perform cataract surgery was at least 6 months after a trabeculectomy, to decrease the risk of bleb failure. Seah et al concurred, stating that the longer the interval between surgical procedures, the better the IOP control. These authors based their conclusion on studies that were retrospective and in which the majority of patients had undergone ECCE. However, the concept that the timing of cataract surgery has an influence on when trabeculectomy fails is credible. The filtering bleb tends to reduce its IOP-lowering effect as time progresses. This effect will be further altered depending on when in its natural history any insult (ie, cataract surgery) takes place. It is therefore crucial to include time from trabeculectomy to cataract surgery in any model examining trabeculectomy failure rates. The difficulty in including the variable “time from trabeculectomy to cataract surgery” is how to classify participants who did not have cataract surgery. Describing the time as “infinity” for such participants is problematic in constructing a statistical model amenable to analysis. We overcame this by entering the reciprocal of time from trabeculectomy to cataract surgery (ie, 1/T) into the model, and therefore were able to assign “zero” for the non–cataract surgery group. In this way, an appropriate statistical model could be used.

To our knowledge, this is the first study that has examined the influence of time from trabeculectomy to cataract surgery on eventual trabeculectomy failure, using an appropriate statistical model. Previous studies on this topic have been noncomparative or have compared pre–cataract surgery IOP with post–cataract surgery IOP. This approach is flawed because it does not account for the natural history of bleb function. Researchers have attempted to account for the natural history of bleb function by comparing participants who have had cataract surgery after trabeculectomy against a matched control group of participants who have had trabeculectomy but did not have subsequent cataract surgery and then comparing IOPs at various time intervals. Although this technique seems like a reasonable approach, the methodology is inadequate in terms of trying to determine the influence of time between surgical procedures on outcomes. Swamynathan et al performed a retrospective analysis of 29 patients who had undergone antimetabolite-augmented trabeculectomy followed by temporal cor-

Table 3. Cox Regression Analysis for Risk Factors for Trabeculectomy Failure

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td>0.981 (0.960-1.003)</td>
<td>.09</td>
</tr>
<tr>
<td>No diabetes</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.166 (0.693-1.962)</td>
<td>.56</td>
</tr>
<tr>
<td>Glaucoma diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open angle</td>
<td>1.726 (1.076-2.770)</td>
<td>.013</td>
</tr>
<tr>
<td>Closed angle</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>No. of pretrabeculectomy antiglaucoma drops</td>
<td>1.044 (0.926-1.772)</td>
<td>.48</td>
</tr>
<tr>
<td>Pre trabeculectomy IOP</td>
<td>1.044 (1.009-1.082)</td>
<td>.015</td>
</tr>
<tr>
<td>No. of postoperative steroid drops</td>
<td>1.072 (0.980-1.173)</td>
<td>.13</td>
</tr>
<tr>
<td>Trabeculectomy augmentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU</td>
<td>1.329 (0.846-2.089)</td>
<td>.22</td>
</tr>
<tr>
<td>Placebo</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Reciprocal of time to cataract surgery</td>
<td>1.731 (1.050-2.854)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; IOP, intraocular pressure; 5-FU, 5-fluorouracil.
neal phacoemulsification. The mean (SD) time between trabeculectomy and phacoemulsification was 14 (8.4) months. This group was matched in terms of length of follow-up and type of antimetabolite used to a group that did not have cataract surgery. The IOPs were compared between the 2 groups at equivalent times after phacoemulsification; the mean follow-up was approximately 20 months. Using failure as an outcome, defined as an IOP of greater than 21 mm Hg or the need for further surgery, Swamynathan et al22 found no difference between the 2 groups. Park et al23 used a similar methodology and a similar definition of failure, in a retrospective study with 40 eyes in each group. Comparing survival curves, they found no difference between the 2 groups. Chen et al27 tried a different approach. They performed a retrospective review of 115 consecutive participants who had undergone trabeculectomy and then went on to have either ECCE or phacoemulsification. Variables were entered into a Cox regression model to determine risk factors for bleb failure. Chen et al concluded that being younger than 50 years of age, having undergone intraoperative iris manipulation, and having an early postoperative IOP of greater than 25 mm Hg were associated with loss of IOP control. The study27 was limited, however, by a loose definition of failure, namely, that failure constituted a need for medication, surgery, or bleb needling conducted at the physician’s discretion.

We also found that participants with open-angle glaucoma had trabeculectomy failure significantly earlier than did participants with PACG. In other words, participants with PACG tended to have better IOP control. One possible explanation is that some of the participants in both groups had cataract surgery and that the cataract surgery might be expected to have a more beneficial role (in terms of IOP control) in patients with PACG than in patients with open-angle glaucoma owing to the opening of the drainage angle. This will be explored in a later study.

Several limitations of our findings should be borne in mind. Participants for this analysis were taken from a randomized trial of 5-FU–augmented trabeculectomy vs placebo that was not designed to answer the study question posed in this analysis and that may therefore have been insufficiently powered to do so. There are many factors that would likely affect trabeculectomy failure rates, but these factors were not examined owing to a lack of data. These factors are mainly concerned with the amount of trauma that occurred during the cataract surgery. Factors such as phacoemulsification technique, time taken to complete surgery, and power of ultrasound used, manipulation of the iris, degree of lens opacity, placement of the paracentesis with regard to bleb location, steroid use after cataract surgery and compliance thereof, and grade of surgeon operating (as a surrogate for amount of trauma induced) are but some of the factors that may affect the analysis. Use of a flare meter during the postoperative period would have been a useful quantitative measure of the amount of surgical trauma induced and would be valuable in future studies. Conversely, the fact that these data were not recorded could be an advantage in that our findings may be of more relevance to real clinical situations. There were no cataract extractions performed in the first 3 months after trabeculectomy, and only 2 surgical procedures were performed in the first 6 months. There is some evidence that cataract surgery, especially that involving conjunctival incisions, results in higher trabeculectomy failure rates if surgery is performed in the first 30 days after trabeculectomy compared with surgery performed more than 90 days after trabeculectomy.24 Because no cataract surgery was performed in the first 3 months after trabeculectomy and because of the limitations of the statistical model that we used, our conclusions may not be valid for cataract surgery performed within a few months of trabeculectomy. Nonetheless, to our knowledge, this is the largest prospective study that has examined the effect of cataract surgery on eyes that have undergone a trabeculectomy. We used an appropriate statistical method to examine this relationship and were able to identify a trend toward earlier trabeculectomy failure in participants who had cataract surgery soon after having undergone trabeculectomy. Delaying cataract surgery in eyes that had a previous trabeculectomy increases the chances of successful IOP control.

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REFERENCES


