Success of trabeculectomy surgery in relation to cataract surgery: 5 year outcomes

<table>
<thead>
<tr>
<th>Journal:</th>
<th>British Journal of Ophthalmology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID</td>
<td>bjophthalmol-2018-312972</td>
</tr>
<tr>
<td>Article Type:</td>
<td>Clinical science</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>30-Jul-2018</td>
</tr>
<tr>
<td>Complete List of Authors:</td>
<td>Mathew, Rashmi; Moorfields Eye Hospital NHS Foundation Trust, Department of glaucoma Parvizi, Sahar; Moorfields Eye Hospital NHS Foundation Trust Murdoch, Ian; The Institute of Ophthalmology, Genetics; Moorfields Eye Hospital,</td>
</tr>
<tr>
<td>Keywords:</td>
<td>Glaucoma, Treatment Surgery, Wound healing</td>
</tr>
</tbody>
</table>
Title: Success of trabeculectomy surgery in relation to cataract surgery: 5 year outcomes

Authors

1) Ms Rashmi G Mathew, FRCOphth (corresponding author)
Consultant Ophthalmologist, Department of Glaucoma,
Deputy Director for Undergraduate Education,
Moorfields Eye Hospital NHSFT, London, EC1v 2PD
Email: Rashmi.mathew@moorfields.nhs.uk
Tel: 020 7566 2625

2) Ms Sahar Parvizi, FRCOphth
Paediatrics Fellow
Moorfields Eye Hospital NHSFT, London, UK, EC1V 2PD

3) Mr Ian E Murdoch, MD, FRCOphth
Consultant Ophthalmologist and Senior Lecturer,
Department Epidemiology and International Eye Health
Institute of Ophthalmology, Genetics
11-43 Bath Street
London, EC1V 9EL
**Synopsis**

Trabeculectomy success at 5 years was similar, in eyes which had trabeculectomy alone, cataract surgery and then trabeculectomy any time afterwards, and trabeculectomy with cataract surgery performed within two years of trabeculectomy.
Abstract:

Aims: To compare success proportions at five years in three surgical groups:
- Group 1: Trabeculectomy alone
- Group 2: Trabeculectomy followed by cataract surgery within 2 years
- Group 3: Trabeculectomy performed on a pseudophakic eye

Methods: A retrospective cohort study. 194 eyes of 194 patients were identified with at least 5-years follow-up post-trabeculectomy (N = 85, 60, 49 in groups 1, 2, 3 respectively).

Main Outcome Measures:
- Primary Outcome Measure: intraocular pressure (IOP) at 5 years post trabeculectomy surgery
- Secondary Outcome Measure: change in visual acuity at 5 years

Results:
At 5 years, the mean IOP (SD) was 12.9 (3.5), 12.5 (4.8), 12.7 (4.8) mmHg in groups 1, 2, 3 respectively. Overall success was almost identical, 58%, 57%, 59%, in groups 1, 2, 3 respectively. There was no significant difference between the groups in terms of percentage IOP reduction, number of medications, proportion re-starting medication, re-operation rates at 5 years. Logistic regression for an outcome of failure, showed males to be at increased risk of failure OR 1.97 (95% CI; 1.10-3.52, p=0.02).

Conclusions:
The sequence in which surgery is carried out does not appear to affect trabeculectomy function at 5 years, success being similar to trabeculectomy alone. In our study males may be at increased risk of failure.
**Introduction:**

Cataract and glaucoma are the two most common causes of preventable blindness in the world.\(^1\) Both are age related, hence often coexist.\(^2\) Treatment of cataract is surgical whereas therapy for glaucoma may be medical, laser or surgical. Trabeculectomy remains the most commonly considered surgical option to lower the intraocular pressure (IOP).\(^3,4\) One third of patients with trabeculectomy require cataract surgery within 2 years.\(^5,6\) This rises to two thirds by 8 years.\(^7\) The question about surgical order of the two procedures is widely debated in glaucoma circles. In terms of trabeculectomy survival should cataract surgery be undertaken prior to or after trabeculectomy?

Success rates of trabeculectomy surgery are difficult to sensibly interpret between studies due to differing study methods and definitions of success and failure. A ‘broad brush’ view of the literature is given below.

**Trabeculectomy**

The large audit by Kirwan et al reports success (IOP ≤18mmHg *and* 20% reduction) at two years as 78% complete and 86% qualified success (N=428 eyes).\(^5\) Quigley et al using the same success criteria at 4 years reported 53% complete and 72% qualified success (N=150 eyes).\(^8\)

**Cataract surgery after trabeculectomy**

In the audit by Kirwan et al 115/376 phakic eyes underwent cataract surgery during the two years post trabeculectomy period. 90/115 (78%) were complete and 99 (86%) partial success at 2 years post trabeculectomy surgery.\(^5\) Whilst not long follow-up after the cataract surgery this does imply little effect on the success of the trabeculectomy surgery (comparing to those with no cataract surgery Chi\(^2\) = 0.002 p=0.96).

Looking at an outcome two years following cataract surgery the literature reports between 10-35% of functional trabeculectomies failing within this period.\(^9\)-\(^17\)

A few studies have looked at the effect of timing of cataract surgery on the success of trabeculectomy surgery. A declining risk has been implicated with longer intervals between the two operations.\(^9,16\)

**Cataract surgery before trabeculectomy**

Nguyen et al reported a study comparing trabeculectomy outcomes in patients with prior cataract surgery to those undergoing cataract surgery post trabeculectomy.\(^18\) All phacoemulsifications were done within one year of the trabeculectomy surgery hence it makes most sense to look at their two year results post trabeculectomy in the two groups. No difference in failure was suggested between the groups (8/30 phacoemulsification then trabeculectomy vs 7/18 trabeculectomy then phacoemulsification failed p=0.522).
Considerable debate concerning timing of the two operations continues. With a view to informing future research in this area we undertook a retrospective cohort study to compare trabeculectomy success at 5 years, in eyes which had trabeculectomy alone, cataract surgery and then trabeculectomy at any time afterwards, and trabeculectomy with cataract surgery performed afterwards within two years of the trabeculectomy.

**Methods:**

We reviewed medical records of cases that had undergone trabeculectomy surgery and had at least five years post-trabeculectomy follow-up. Eyes with acute angle closure, juvenile / congenital glaucoma and rubeotic glaucoma were excluded. Those with any previous intraocular surgery other than cataract surgery (e.g. vitreoretinal, glaucoma, cornea, trauma, as well as phaco-trabeculectomy) were also excluded.

If both eyes of one individual were eligible then the eye with the more recent trabeculectomy was chosen for inclusion. Cases were divided into 3 groups (figure 1):

- **Group 1:** Trabeculectomy with no cataract surgery
- **Group 2:** Trabeculectomy followed by cataract surgery within 2 years of the trabeculectomy (cataract after trabeculectomy)
- **Group 3:** Trabeculectomy performed on a pseudophakic eye (the cataract surgery could have been performed at any time prior to the trabeculectomy; cataract before trabeculectomy)

The primary outcome was trabeculectomy success at five years. The definitions of complete success, qualified success and failure are given below:

**Complete success:** a 20% reduction of intraocular pressure (IOP) \(\text{and } \text{IOP} \leq 18\text{mmHg}\) without the need for IOP lowering therapy or further surgery at 5 years post trabeculectomy.

**Qualified success:** a 20% reduction of IOP \(\text{and } \text{IOP} \leq 18\text{mmHg}\) with topical intraocular pressure lowering treatment alone.

**Failure:** IOP not reduced by 20% \(\text{or } \text{IOP} > 18\text{mmHg}\) with topical therapy \(\text{and/or a need for reoperation including a revision for clinically significant hypotony, redo trabeculectomy, aqueous shunt surgery, or cyclodiode ciliary body ablation undertaken within 5 years of the original trabeculectomy.}\)

Bleb needling and post-operative subconjunctival injections of steroid and/or 5-fluorouracil were considered part of normal post-operative care.

The secondary outcome measure was change in visual acuity, defined as a change by two or more lines of vision on a Snellen chart at 5 years post trabeculectomy as compared to baseline acuity.

**Sample size**
Considering the exposure of cataract surgery, a sample size of 79 unexposed (group 1) and 40 exposed (group 2 or group 3) would show a reduction in success proportion from 80% to 55% with 95% confidence and 80% power (Fleiss calculation Epi-Info v7).

**Data analysis**

Data was collected on a standardised proforma (Microsoft Excel spreadsheet) The outcomes of visual acuity and intraocular pressure were recorded at multiple time points.

In addition data was collected on age, gender, laterality, previous ocular history, diagnosis, new ocular pathology, number and time on topical ocular hypotensive drops, laser therapy, surgical details, operative complications, duration of post-operative topical steroid use, bleb needling procedures and further surgery.

Data was analysed using both istata v7.0 for Windows (http://www.stata.com) and GraphPad Prism Version 6.0d (GraphPad Software, Inc). Contingency tables were assessed for symmetry using Chi squared analysis, and continuous variables compared using a two tailed t-test. Logistic regression was undertaken investigating risk factors for the primary outcome. A p-value of less than 0.05 was considered statistically significant.

The study was approved by the Clinical Audit unit, research and development department at Moorfields Eye Hospital. Analyses of this type do not require individual ethical permission as they are viewed as audit (see http://www.hra.nhs.uk/research-community/before-you-apply/determine-whether-your-study-is-research/). The study was conducted in accordance with the Declaration of Helsinki, and the UK Data Protection Act.

**Results:**

A total number of 194 eyes (102 right) of 194 patients (92 female) were included. The baseline demographic details are shown in table 1.
Table 1. Baseline demographic details. POAG: primary open angle glaucoma; PXF: pseudoexfoliative glaucoma; PDG: pigment dispersion glaucoma; OHT: ocular hypertension.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IOP (mmHg) SD</td>
<td>23.4 (8.7)</td>
<td>24.4 (9.8)</td>
<td>24.2 (8.0)</td>
</tr>
<tr>
<td>Mean number of medications</td>
<td>2.71</td>
<td>2.62</td>
<td>2.78</td>
</tr>
<tr>
<td>Time on medicines prior to trabeculectomy in years (n=77;57;46) mean (SD) (range)</td>
<td>11.1 (SD 8.0) (0 to 33)</td>
<td>+6.8 (SD 5.7) (0 to 21.7)</td>
<td>11.1 (SD 6.1) (0.5 to 27.4)</td>
</tr>
</tbody>
</table>

Group 3 were significantly older than groups 1 and 2; t-test Group 3 vs Group 1 (P=0.0006); Group 3 vs Group 2 (P=0.005). Patients were on topical and/or oral IOP lowering treatment for an average of 11 years before having trabeculectomy surgery in groups 1 and 3. Those who had had cataract surgery after trabeculectomy were on medical therapy for an average of 7 years, which is significantly less, when compared to the other two groups (t-test comparing group 2 with Group 1 p<0.001 and Group 3 p<0.001).

The findings by group are shown in Table 2. The mean IOP reduced from 23.4, 24.4, 24.2mmHg to 12.9, 12.5,12.7mmHg in groups 1,2 and 3 respectively at 5 years. The overall success was 58%, 57% and 59% in groups 1,2,3 respectively. The mean number of medications reduced from 2.71, 2.62, 2.78 to 1.0,1.4 and 1.3 across the 3 groups. There was no difference in the proportion of patients restarting medication, undergoing repeat surgery for insufficient IOP control or hypotony between the groups.

<table>
<thead>
<tr>
<th></th>
<th>Trabeculectomy alone Group 1 n=85</th>
<th>Cataract after trabeculectomy Group 2 n=60</th>
<th>Cataract before trabeculectomy Group 3 n=49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IOP (mmHg)</td>
<td>12.9 (SD 3.5)</td>
<td>12.5 (SD 4.8)</td>
<td>12.7 (SD 4.8)</td>
</tr>
<tr>
<td>Percent IOP change at 5 years compared to pre trabeculectomy mean IOP% change (SD) (range)</td>
<td>-38.8% (SD 24.7) (36 to -80%)</td>
<td>-41.4% (SD 31.8) (60 to -88.9%)</td>
<td>-43.3% (SD 24.7) (29 to -92%)</td>
</tr>
<tr>
<td>Complete success (≥20% IOP drop and IOP ≤18mmHg)</td>
<td>33 (39%)</td>
<td>24 (40%)</td>
<td>21 (43%)</td>
</tr>
<tr>
<td>Qualified success (≥20% IOP drop on medication + IOP)</td>
<td>16 (19%)</td>
<td>10 (17%)</td>
<td>8 (16%)</td>
</tr>
</tbody>
</table>
Table 2. Outcomes for each surgical group at 5 years. No results showed a statistical difference between groups.

Logistic regression was undertaken for an outcome of failure (see table 3). Failure definition being, IOP not reduced by 20% or IOP > 18mmHg with topical therapy and/or a need for reoperation including a revision for clinically significant hypotony, redo trabeculectomy, aqueous shunt surgery, or cyclodiode ciliary body ablation undertaken within 5 years of the original trabeculectomy). The results do not suggest major confounding and mirror the results of the contingency tables. There was a gender difference, male patients being more at risk of failure (multivariate OR 1.95 p=0.04). In view of the possibility of early differences we examined outcomes at each yearly interval and there was no pattern of more rapid failure in any one particular group.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Univariate OR (95% CI, p)</th>
<th>Multivariate OR (95% CI, p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at trabeculectomy</td>
<td>0.985 (0.964-1.007, p=0.190)</td>
<td>0.989 (0.963-1.015, p=0.396)</td>
</tr>
<tr>
<td>Gender</td>
<td>1.968 (1.101-3.518, p=0.022)</td>
<td>1.950 (1.043-3.646, p=0.037)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>0.727 (0.385-1.371, p=0.325)</td>
<td>0.923 (0.463-1.843, p=0.821)</td>
</tr>
</tbody>
</table>
Cataract surgery following trabeculectomy was complicated by vitreous loss in 3 cases two of which failed and the remaining case was a partial success at 5 years. Both the mean and median time to cataract surgery after trabeculectomy was 1.2 years (range 0.3-2.0; SD 0.5 years). Seventeen had 5-FU used at the time of cataract surgery or in the immediate post-operative period. There was no statistical difference in overall success between those with and without cytotoxic use ($\chi^2 = 2.54$, $p=0.11$).

The secondary outcome measure of visual acuity change at 5 years post-trabeculectomy, showed nearly 80% of patients retained or improved their vision following their initial trabeculectomy. Table 4 illustrates the visual acuity changes of two Snellen lines or more at 5 years compared to pre-trabeculectomy acuities within each group. The visual acuity was significantly better in group 2 at years and overall $\chi^2 = 20.6$, $p=0.0004$. It should be noted that Group 3 were a significantly older group, with more ocular co-morbidity.

<table>
<thead>
<tr>
<th></th>
<th>Trabeculectomy alone (n=83)</th>
<th>Cataract surgery within 2 years of trabeculectomy (n=60)</th>
<th>Cataract surgery before trabeculectomy (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA worse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\chi^2=7.26$ $p=0.26$</td>
<td>20.5% (17/83)</td>
<td>10.0% (6/60)</td>
<td>30.6% (15/49)</td>
</tr>
<tr>
<td>(n=38)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA same</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\chi^2=2.53$ $p=0.28$</td>
<td>79.5% (66/83)</td>
<td>76.7% (46/60)</td>
<td>67.4% (33/49)</td>
</tr>
<tr>
<td>(n=145)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Secondary outcomes measure of change in visual acuity at year 5 after trabeculectomy surgery as compared to baseline. At least two lines of vision (Snellen) gained or lost was used to define ‘better’ and ‘worse’ respectively.

Discussion:

We report a retrospective cohort study comparing trabeculectomy success at 5 years, in eyes which had trabeculectomy alone, cataract surgery and then trabeculectomy at any time afterwards, and trabeculectomy with cataract surgery performed afterwards within two years of the trabeculectomy. Our findings have not suggested any major difference between the three groups.

The overall success proportion for our combined data at five years was 58% (95% CI 51-65%). This is lower than those reported by Jampel et al and the Singapore 5 FU trial. Jampel et al found 72% (95% CI 66-78%) at 4 years for the same outcome definition. It could be that the extra year of follow-up in our study, accounts for some additional attrition in success proportion. In the Singapore study an overall success proportion of 73% (95% CI 66-79%) was found at 8 years, this study had the same IOP cut-off however did not include the 20% reduction criterion. The complete success proportion was similar to our study 45% (95% CI 37-55%). Another explanation for the lower success proportion in our study could be an element of selective bias in our sample. Failing trabeculectomies are more likely to have frequent review. Their notes might therefore be more readily accessible for study inclusion.

As outlined in the introduction, the literature reports variable findings with ordering of cataract and trabeculectomy surgery. There is a prevalent clinical impression that subsequent cataract surgery negatively impacts on trabeculectomy survival. Our finding of no difference in failure proportions between trabeculectomy and trabeculectomy followed by cataract extraction is in agreement with the other reports in the literature. The Singapore 5FU trial reported no difference between those with functional trabeculectomies and subsequent cataract surgery (failure 22% (95%CI 15-32%) at median 5 years) and those with no cataract surgery (failure 27% (95%CI 20-36%) at median 5 years). Ehnrooth et al reported a higher failure proportion in those with subsequent cataract surgery, however they included trabeculectomies that had failed prior to the cataract surgery. If those are excluded from the analysis the difference becomes smaller; functional trabeculectomies and subsequent cataract surgery (failure 44% (95%CI 28-61%)) and those with no cataract surgery (failure 31% (95%CI 22-41%)). Swamynathan et al reported no major difference in success proportions between trabeculectomy and trabeculectomy followed by cataract extraction.

Clinicians generally believe that if cataract surgery is necessary it impacts less on trabeculectomy survival if undertaken first. Our finding of no difference in failure proportions whether cataract surgery is undertaken before or after trabeculectomy is in
agreement with the findings reported by Nguyen et al.\textsuperscript{18} They found trabeculectomy followed by cataract extraction (failure 39\% (95\% CI 20-61\%)) and cataract surgery followed by trabeculectomy surgery (failure 27\% (95\% CI 14-45\%)).

Alternative reasons for our finding of no difference could include:

- Age – group 3 were significantly older. If prior cataract surgery was a risk factor for failure and increasing age a protective factor for failure of subsequent trabeculectomy this might explain a negative finding. The logistic regression however, did not suggest this to be the case.
- Gender – male gender was found to be a risk factor for failure. Other studies have not found this association and we do not have an explanation. One possible reason might be compliance, but this was not assessed.
- Time on medications prior to surgery has been reported as a risk factor for failure although not as powerful as cumulative years of therapy.\textsuperscript{19} We did not collect data on cumulative years of therapy. Group 2 had a significantly shorter duration on topical therapy prior to trabeculectomy surgery. This might have been protective against failure and masked an adverse effect of cataract surgery following trabeculectomy. The multivariate modelling however did not suggest this to be the case.
- It has previously been reported that timing of cataract surgery after trabeculectomy has an effect on trabeculectomy function; longer duration between the surgeries being protective.\textsuperscript{9,16} Our analysis did not suggest this. Hussain et al advocated the use of a reciprocal of the time to cataract surgery post-trabeculectomy for investigation of time relationship to failure.\textsuperscript{9} We undertook this analysis assigning a value of 0 to the trabeculectomy only group and excluding the cataract surgery prior to trabeculectomy group. This did not show any time relationship $p=0.874$. To match this paper, we also looked at those with cataract surgery ≤6 months, 6-12months and >12 months post trabeculectomy. 1/3, 9/15 and 24/42 failed respectively ($\chi^2 = 0.737$, $p=0.692$).

Of the 3 cases with vitreous loss in Group 2, 2 had failed at 5 years, and 1 case was a partial success. The finding that vitreous loss has an adverse effect on outcome is well reported.\textsuperscript{16,20}

The merit of perioperative cytotoxic use in cataract surgery following trabeculectomy is uncertain. Shahid and Salmon found no benefit of 5FU given post-operatively.\textsuperscript{21} Sharma found a beneficial effect from perioperative 5FU at the time of cataract surgery.\textsuperscript{22} Both studies had relatively small numbers. In our study the 5FU was administered at the time of cataract surgery but was found to have no effect. An explanation might be case selection bias for the use of 5-FU. If used in those cases felt most likely to fail, any positive effect might be masked.

The secondary outcome measure of visual acuity change at 5 years post-trabeculectomy, showed nearly 80\% of patients retained or improved their vision following their initial trabeculectomy. Unsurprisingly a greater proportion of Group 2 had improved vision over the five years following trabeculectomy surgery. Over this time period the order of worsening vision was; group 2 < group 1 < group 3. An
explanation for group 1 being worse than group 2 may be cataract progression post trabeculectomy.\textsuperscript{2} With respect to the worst acuity in group 3, these were an older group with known greater ocular co-morbidity.

\textit{Study limitations}

There are two potential limitations to this pilot study. Firstly, as a retrospective study there is potential for unquantifiable bias. For example the most accessible notes may be more biased towards failures (both IOP and visual) which would be seen more frequently in the clinics. However such bias would apply to all groups hence be non-selective. Secondly our study sample size is powered to detect a large effect in terms of difference in failure proportions. A question then arises as to the clinical importance of finding a smaller effect.

\textit{Conclusions}

Cataract and glaucoma often co-exist and their surgical management can be challenging. This study looks at the impact of cataract surgery on trabeculectomy function and whether the order of surgery affects trabeculectomy survival. We found no difference in trabeculectomy survival between the 3 comparator groups at 5 years. This is in broad agreement with the available literature on this topic.

\textit{Acknowledgments:}

We would like to thank Sally Ameen and Naomi Tan for their contribution to case note identification and Lin Lu for her contribution to data entry.

\textit{References}

1) \url{http://www.who.int/blindness/causes/en/}
Figure 1. Outline of the three study groups and the timing of cataract surgery, in relation to trabeculectomy surgery.