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The Norwich Trabeculectomy Study: Long-term Outcomes of Modern Trabeculectomy with Respect to Risk Factors for Filtration Failure

David C Broadway[1-3*] **and Allan Clark**[2]

[1]*Norfolk and Norwich University Hospital, Colney Lane, Norwich NR4 7UY, UK*

[2]*The Norwich Medical School, Norwich Research Park, University of East Anglia, Norwich NR4 7TJ, UK*

[3]*The Schools of Biological Science and Pharmacy, Norwich Research Park, University of East Anglia, Norwich NR4 7TJ, UK*

[*]**Corresponding author:** Professor David C Broadway BSc (Hons) MD FRCOphth DO(RCS), Department of Ophthalmology, Norfolk & Norwich University Hospital, Colney Lane, Norwich, Norfolk, NR4 7UY, United Kingdom, Tel: +441603 288373; Fax: +441603 288261; E-mail: david.broadway@nnuh.nhs.uk

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Abstract

Objective: The aim of the study was to evaluate the long-term outcomes of a large series of 'modern' trabeculectomies with specific respect to traditional risk factors for failure.

Methods: 636 consecutive 'modern', augmented 'safe-technique' trabeculectomies performed over an 11-year period (1998-2008) were assessed in a single centre, observational, cohort study. Traditional risk factors for failure (previous surgery, long-term exposure to topical medication, young age, secondary glaucoma and trainee surgeon) were assessed using various success outcome criteria. Success survival was defined with respect to various intraocular pressure (IOP) targets, using criteria for both complete and two categories of qualified success. A multivariate logistic regression analysis was performed to account for the significant number of patients with more than one risk factor.

Results: The mean follow-up period was 65.5 (± 35.7) months. At final follow-up the mean IOP for all eyes was reduced from 23.4 (± 6.2) mmHg pre-operatively to 11.9 (± 4.2) mmHg ($p<0.001$) and the mean number of topical anti-glaucoma medications was reduced from 2.3 to 0.4 ($p<0.001$). Complete success rates were 65% (IOP ≤ 15 mmHg, no medications) and 71% (IOP ≤ 21 mmHg, no medications) at final follow-up. Qualified success rates varied from 78% to 97%, depending on IOP threshold. Outcomes for the various risk factor groups were compared with a 'risk-free' control group. Overall, traditional risk factors for failure did not significantly influence outcome for the various success criteria, but surgery performed by trainee surgeons had less satisfactory outcomes compared to surgery performed by a more senior surgeon. Clinic-based post-operative interventions were more frequently required in eyes with 'traditional' risk factors for failure.

Conclusions: In a large cohort of mainly Caucasian patients, appropriately augmented, 'modern', 'safe-technique' trabeculectomy was highly successful and, together with 'modern' post-operative management, appeared to annul the effect of most 'traditional' risk factors for failure such as previous surgery, long-term exposure to topical medication, relative youth and secondary glaucoma.

Keywords: Trabeculectomy; Risk factors for failure; Mitomycin-C; 5-Fluorouracil; Post-operative management; Bleb needling; Adjustable/releasable sutures

Introduction

The term trabeculectomy was first coined by Sugar in 1961 [1], described by Korrylos in 1967 [2], popularised by Cairns and Phillips in 1968 [3,4] and further promulgated by Linnér in 1969 [5] and Watson in 1970 [6]. Since 1970 trabeculectomy has become the most commonly used surgical procedure for lowering intraocular pressure (IOP). A number of modifications have been introduced, and accepted by many surgeons, in an attempt to improve success and reduce complications. Modifications have included improved instrumentation, the use of antifibrotic agents (5-fluorouracil [5-FU] or mitomycin-C [MMC]), the placement of adjustable/releasable scleral flap sutures [7,8], more intensive post-operative management [9] and fellowship training. Modern safe-technique trabeculectomy has been made fashionable by Khaw [10] and favourable results have been published [11-13].

A number of risk factors for failure of trabeculectomy have been identified [14] and include previous ocular surgery [15,16], secondary glaucoma [17,18], young age [19], previous long-term exposure to topical anti-glaucoma medications [20,21], black race [22], diabetes [23,24], surgeon inexperience [23] and various peri-operative ocular factors such as high pre-operative IOP [24], sub-conjunctival anaesthetic [23], use of a superior rectus traction suture [23], marked post-operative inflammation [24] and significant post-operative complications [24]. Most risk factors for failure of trabeculectomy were identified before the introduction of the 'safe-technique', augmented, trabeculectomy [10]. The aim of the present study was to determine the effect of 'traditional' risk factors for filtration failure on the success of 'modern' trabeculectomy.

Materials and Methods

Participants: Institutional review board approval was obtained by the Research and Development Audit Department of the Norfolk and Norwich University Hospital. The study adhered to the tenets of the Declaration of Helsinki. All trabeculectomies performed under the care of one of the authors (DCB) between 1998 and 2008 (n=650) were included. Data was collected prospectively on clinic sheet proformas and subsequently transferred onto a computer spreadsheet for subsequent analysis. Insufficient data was collected from 14 cases since patient charts were lost in a flood incident, leaving 636 trabeculectomies for analysis. Data collected included: baseline patient demography and follow-up data for 1 day, 1 week, 1 month, 3, 6 and 12 months and annually thereafter until the final visit (visual acuity [VA], IOP, topical anti-glaucomatous therapy, complications, bleb manipulation, 'new' co-morbidity such as cataract or macular degeneration, additional ophthalmic procedure). Patient ethnicity was classified as white-British, Afro-Caribbean or Asian. Glaucoma diagnoses were classified as Primary Open Angle (POAG), Normal Tension (NTG), chronic Primary Angle Closure (PACG), Acute Angle Closure (AACG), Pseudoexfoliative (PXG), Pigmentary (PG), Secondary (SG) or Congenital (CG) Glaucoma and Glaucoma Suspect/Ocular Hypertension (GS/OH). NTG was defined as previously described in the Collaborative NTG Study [25] and the high-tension diagnoses by standard clinical definitions [26].

Ophthalmic data: Anti-glaucomatous therapy for each eye was documented at all time-points in terms of number of agents. Previous topical therapy was dichotomised as to whether the eye had been subjected to <3 years or ≥ 3 years of topical therapy prior to trabeculectomy. Surgeon status was defined as either consultant or trainee. Anaesthesia was defined as either general or local and local anaesthesia was sub-divided into peri-bulbar/sub-Tenon or sub-conjunctival.

Trabeculectomy was performed using the same technique for all cases, as described elsewhere [10]. 5-FU or MMC were utilised on the basis of a clinical decision with respect to perceived risk of trabeculectomy failure (low/moderate/high) [10], pre-operative state of the conjunctiva [14] and in cases where the fellow eye was undergoing surgery, the result and bleb appearance of the earlier contralateral trabeculectomy. Per-operative sub-conjunctival 5-FU was used at a concentration of 25 mg/ml (Hospira, Leamington Spa, UK) and MMC at concentrations of either 0.2 mg/ml or 0.4 mg/ml (ProStrakan, Galashiels, UK), delivered into the sub-conjunctival space soaked into polyvinyl sponges (Merocel, Medtronic Xomed, Jacksonville, USA) for durations varying from 1-5 min. In most cases exposure time for 5-FU was 5min and for MMC was 3 min, the duration being determined on the basis of perceived risk of trabeculectomy failure [10]. In a minority of cases augmentation with per-operative antifibrotic was not deemed necessary.

Outcomes: Surgical success was defined and classified using criteria based on World Glaucoma Association (WGA) guidelines [27]. Success was considered 'complete' if no additional medication or bleb needling was required and 'qualified-1' if additional medication (but no bleb needling) was required (criterion 1) or 'qualified-2' if additional medication and/or bleb needling was required (criterion 2). IOP thresholds of ≤ 21 mmHg, ≤ 18 mmHg, and ≤ 15 mmHg were used in the definitions of surgical success, as was a reduction from the pre-operative IOP of ≥ 20%, ≥ 25% or ≥ 30%, these percentage criteria being of particular importance with respect to eyes with NTG. Combinations of absolute IOP level with %-reduction in IOP were used to compare results with other published studies and avoid any bias [28]. Eyes with post-operative IOP values of <6 mmHg were not classified as failure providing the relative degree of hypotony was not associated with a reduction in Snellen VA of >1 line due to any adverse consequences of low IOP [29].

Surgical failure was considered to have happened if the criterion for success on the basis of IOP were not met on 2 consecutive follow-up visits, if further glaucoma filtration surgery or laser therapy was performed or if the eye developed irreversible 'blindness', considered to be a result of the trabeculectomy (eg expulsive haemorrhage), rather than 'new' co-morbidity (eg macular degeneration), there being a reduction in Snellen VA to 'counting fingers (CF)' or worse, unless the pre-operative VA was ≤ 6/60, when 'blindness' was defined as progression to 'no perception of light' [27]. Bleb needling performed within the first 3 post-operative months was not a criterion for defining trabeculectomy failure, whereas needlings performed after 3 months were. Most bleb needling procedures were augmented with either a sub-conjunctival injection of 5 mg 5-FU or trans-conjunctival application of 0.5 mg/ml MMC for 5 min. All bleb needlings (and their augmentation) were documented and the total number of bleb needling procedures per case, or group, analyzed. Bleb revision surgery to reduce bleb size in cases where dysaesthesia was a complication was not considered within the criteria for defining trabeculectomy failure.

Risk factors for failure: The 'traditional' risk factors for trabeculectomy failure considered were previous ocular surgery, re-do trabeculectomy, long-term exposure to topical medication, young age, secondary glaucoma and trainee surgeon. For risk factor sub-group comparative analysis, the previous surgery group of eyes included those that had undergone previous intraocular surgery and/or surgery involving conjunctival incision, but excluded eyes undergoing re-do trabeculectomy, those with secondary glaucoma, patients ≤ 55 years of age and cases performed by trainee surgeons. The group of re-do trabeculectomies included all cases undergoing a second trabeculectomy and those undergoing trabeculectomy following a phako-trabeculectomy. The group considered at increased risk of failure due to topical medication exposure included eyes with drop exposure >3 years, but excluded eyes that had undergone previous surgery (including re-do trabeculectomies), had secondary glaucoma, had surgery performed by a trainee or were in patients ≤ 55 years of age. The young patient group of eyes included all trabeculectomies in patients ≤ 55 years of age, but excluded eyes undergoing re-do trabeculectomy and/or those with secondary glaucoma. The secondary glaucoma group of eyes included all eyes with secondary glaucoma apart from those undergoing re-do trabeculectomy. The trainee surgeon group included eyes undergoing trabeculectomy by trainees, but excluded eyes with known major risk factors (secondary glaucoma, previous ocular surgery and/or age ≤ 55 years). A 'risk-free' control group of eyes included those that had not undergone any form of previous ocular surgery of laser procedure, had primary glaucoma and had been exposed to <3 years of topical medication, had surgery performed by the consultant and were white-British patients >55 years old.

For groups of patients with defined risk factors for failure, surgical success was compared with respect to various intraocular pressure (IOP) targets, using criteria for both complete and two categories of qualified success (as recommended by the WGA guidelines) [27]. In addition, a multivariate logistic regression analysis was performed to account for the significant number of patients with more than one risk factor.

Statistical analysis: Stata/SE 11.2 Data analysis and statistical software (Texas, USA) was used for descriptive and inferential statistics. For the multivariate statistical analysis potential risk factors for success/failure of trabeculectomy were identified via a logistic regression model. Factors were selected using forward selection criteria. Potential risk factors were age as a continuous variable and others (pre-operative IOP, presenting IOP, diagnosis, duration of previous topical therapy [<3/≥ 3 years], surgeon status [consultant/trainee], glaucoma diagnosis, use of topical therapy, if surgery was a re-do, previous surgery and antifibrotic usage) as categorical variables. Test statistics, odds ratios, 95% confidence intervals (CI) and p values were determined. P<0.05 was considered statistically significant. Statistical analysis was performed using the first eye only and then both eyes for patients that had bilateral surgery, but since the findings were no different, only the results for all eyes are presented. The use of a robust variance estimator allowed for the correlation of outcomes within patients. Factors were compared between groups using Mann-Whitney tests for continuous variables and chi-squared tests for categorical variables. To allow for varying follow-up durations, Kaplan-Meier curves were estimated for the time until failure. Comparisons were based on a Cox-proportional hazards regression model, with an allowance for the correlation between eyes within a patient, by using a robust variance estimator.

Results

A total of 507 patients undergoing 636 consecutive trabeculectomies performed over an 11-year period (1998-2008) were included, having a minimum follow-up of 2 years. Bilateral surgery was carried out in 129 patients. Patient demography is shown in Table 1 and ocular data in Table 2. The mean follow-up period was over 5 years, maximum follow-up being 13 years. At presentation, prior to any therapy, mean IOP for all eyes had been 30.2 (± 9.3; range: 15-76) mmHg. At final follow-up the mean IOP for all eyes was reduced from 23.4 (± 6.2; range: 12-60) mmHg pre-operatively to 11.9 (± 4.1; range: 1-42) mmHg (p<0.001) and the associated mean number of topical anti-glaucoma medications was reduced from 2.3 (± 1.1; range: 1-5) to 0.4 (± 0.9; range: 1-4) (p<0.001). For the whole cohort of eyes complete success rates at final visit were 71%, 69% and 65%, for the IOP thresholds of ≤ 21 mmHg, ≤ 18 mmHg and ≤ 15 mmHg respectively.

	Patients (n=507)	Eyes (n=636)
Mean age [years] (± SD; range)	69.2 (±11.3; 11-91)	69.3 (±11.0;11-91)
Gender M/F [n]	238/269	287/349
Race [n]		
White-British	495	622
Afro-Caribbean	8	10
Asian	4	4
SD: Standard Deviation; M: Male; F: Female; n: Number		

Table 1: Patient demography.

With respect to IOP reductions from pre-operative IOP of ≥ 20%, ≥ 25% or ≥ 30%, complete success rates were 69%, 68% and 66% respectively. The mean %-drop in IOP for the whole cohort was 47% and the maximum drop achieved was 97%. For the whole cohort of eyes qualified success (criterion 1) rates were 90%, 85%, and 79%, for the IOP thresholds of ≤ 21 mmHg, ≤ 18 mmHg and ≤ 15 mmHg respectively. With respect to IOP reduction from the pre-operative IOP of ≥ 20%, ≥ 25% or ≥ 30% qualified success (criterion 1) rates were 84%, 82% and 78% respectively. For the whole cohort of eyes qualified success (criterion 2) rates were 97%, 93%, and 84%, for the IOP thresholds of ≤ 21 mmHg, ≤ 18 mmHg and ≤ 15 mmHg respectively. With respect to IOP reduction from the pre-operative IOP of ≥ 20%, ≥ 25% or ≥ 30% qualified success (criterion 2) rates were 93%, 89% and 86% respectively.

Diagnosis [number of eyes / %]	
Primary Open Angle Glaucoma	398 (62.6%)
Normal Tension Glaucoma	88 (13.8%)
Pseudoexfoliative Glaucoma	15 (2.4%)
Pigmentary Glaucoma	4 (0.6%)
Glaucoma Suspect / Ocular Hypertension	9 (1.4%)
Primary Angle Closure Glaucoma	66 (10.4%)
Acute Angle Closure Glaucoma	8 (1.3%)
Secondary Glaucoma	46 (7.2%)
Congenital Glaucoma	2 (0.3%)
Surgeon status [number of eyes]	
Consultant	534 (84%)
National Health Service	- 396 (62%)
Private	- 138 (22%)
Trainee	102 (16%)
Fellow	- 40 (6%)
Resident	- 62 (10%)
Anaesthesia [number of eyes]	
Peribulbar/Sub-Tenons	477 (75%)
Sub-conjunctival	34 (5%)
General	125 (20%)
Antifibrotic [number of eyes]	
None	75 (11.8%)
5-Flourouracil (1-5 min)	259 (40.7%)
Mitomycin-C (0.2 mg/ml; 1-3 min)	286 (45%)
Mitomycin-C (0.4 mg/ml; 1-3 min)	16 (2.5%)

Table 2: Pre- and per- operative ocular data.

Logistic regression multivariate modeling for the whole cohort (Tables 3a-3c) showed that a higher immediate pre-operative IOP had a statistically significant negative effect on success for all criteria used except complete success at the ≤ 21 mmHg threshold. Exposure to topical anti-glaucomatous therapy for >3 years had a positive effect on complete success at the ≤ 15 and ≤ 21 mmHg threshold levels, but no effect for other success criteria. Surgery performed by a trainee was a significant risk factor for failure for all success criteria, except qualified success (criterion 2) at the ≤ 18 and ≤ 21 mmHg threshold levels. Cases carried out within the private healthcare system had a greater chance of complete success and qualified success (criterion 1), but this factor did not influence qualified success (criterion 2). The use of per-operative MMC had a significant positive effect on success, but only for complete success at the ≤ 15 mmHg threshold level.

(a)						
Risk factor	IOP≤21 mmHg	p	IOP≤18 mmHg	p	IOP≤15 mmHg	p
>3 years of pre-op therapy	1.72 (1.08-2.73)	0.02	1.62 (1.04-2.51)	0.04	-	-
Pre-op IOP	-	-	0.97 (0.94-1.00)	0.02	0.96 (0.93-0.99)	0.01
Trainee surgeon	0.54 (0.34-0.88)	0.01	0.53 (0.33-0.85)	0.002	0.58 (0.36-0.93)	0.02
Private case	3.81 (1.95-7.42)	<0.0001	3.00 (1.62-5.58)	0.001	2.29 (1.32-3.99)	0.003
Mitomycin-C	-	-	-	-	1.78 (1.01-3.14)	0.04
(b)						
Risk factor	IOP≤21 mmHg	p	IOP≤18 mmHg	p	IOP≤15 mmHg	p
Pre-op IOP	0.96 (0.92-1.0)	0.03	0.95 (0.92-0.98)	0.001	0.93 (0.9-0.96)	<0.0001
Trainee surgeon	0.48 (0.25-0.9)	0.02	0.46 (0.26-0.81)	0.007	0.43 (0.26-0.72)	0.001
Private case	3.33 (1.14-9.71)	0.03	2.34 (0.99-5.51)	0.05	-	-
(c)						
Risk factor	IOP≤21 mmHg	p	IOP≤18 mmHg	p	IOP≤15 mmHg	p
Pre-op IOP	0.93 (0.89-0.98)	0.006	0.93 (0.9-0.97)	<0.0001	0.93 (0.9-0.96)	<0.0001
Trainee surgeon	-	-	-	-	0.42 (0.24-0.73)	0.002
IOP: intraocular pressure						

Table 3: Statistically significant risk factor odds ratios for success/failure of trabeculectomy identified by logistic regression multivariate modeling for (a) complete success (no topical therapy, no bleb needling), (b) qualified success 1 (± topical therapy, no bleb needling), (c) qualified success 2 (± topical therapy, ± bleb needling).

Overall there were no significant differences when the analyses were carried out using the absolute IOP, %-reduction in IOP or both criteria for success. In studies of this nature, use of %-reduction in IOP is of particular value when including eyes with NTG. However, for the sub-group of 88 eyes with NTG at their final visit the mean %-reduction in IOP from the pre-operative level was 46.1%, this being no different, statistically, to the reduction for eyes with high-tension glaucoma (47.3%). For the 88 eyes with NTG, follow-up was for a mean of 60 (± 32; 12-134) months and at the final visit the mean IOP achieved was 9.9 (±2.8; 5-16) mmHg with a mean number of topical medications of 0.34, used in 19.3% of the eyes. Bleb needlings had been carried out in 18.2% of eyes with NTG (mean 0.36, range 0-5). For subsequent analyses, results relating to absolute IOP levels were utilised.

Complications are summarised in Tables 4a and 4b. There were no cases of endophthalmitis. There was a greater tendency for trainee surgeon cases to develop early post-operative hypotony (low IOP, shallow anterior chamber, choroidal effusion and maculopathy). In general, however, there were no significant differences in the complication rates for the risk factor subgroups.

Complication [n (%)]	45 (43 eyes; 6.8%)
Conjunctival tear needing additional suture	13 (2%)
Sub-conjunctival haemorrhage	11 (1.7%)
Hyphaema	7 (1.1%)
Vitreous to sclerostomy needing anterior vitrectomy	6 (0.9%)
Scleral patch graft needed during re-do surgery	5 (0.8%)
Anterior chamber penetration by traction suture	2 (0.3%)
Choroidal haemorrhage	1 (0.2%)

Table 4a: Per-operative complications.

n=eyes	**Complication**	**n (%)**
High clinical significance	Choroidal haemorrhage	2 (0.3%)
	Malignant glaucoma	2 (0.3%)
	Total hyphaema	1 (0.2%)
	Flat anterior chamber Serous retinal detachment	1 (0.2%) 2 (0.3%)
	Total filtration failure	1 (0.2%)
	Wipe-out (late)	1 (0.2%)
Common	Hyphaema	85 (13.4%)
	Bleb leak	84 (13.2%)

n=eyes	Complication	n (%)
	Shallow anterior chamber	60 (9.4%)
	Choroidal effusions	76 (11.9%)
	Corneal abrasion	21 (3.3%)
	Sub-conjunctival haem.	18 (2.8%)
	Hypotony maculopathy	33 (5.2%)
	Mega-bleb / dysaesthesia	10 (1.6%)
	Tenon's capsule cyst	15 (2.4%)
Other / rare (<0.5%) and minor	astigmatism, clot in osteum, iris to osteum, pupil distortion, corneal oedema, loose or prominent sutures, vitreous haemorrhage, keratopathy, synechiae, high bleb vascularity, transient blebitis	25 (3.9%)

Table 4b: Post-operative complications.

The consultant performed 534 trabeculectomies, 74% under the National Health Service and 26% in the private sector. Trainees performed 102 of the trabeculectomies, 39% by glaucoma fellows and 61% by residents. Sixty-seven eyes met the criteria as 'risk-free' control cases and the demography for this group and the risk-positive sub-groups is shown in Table 5. Ethnic origin was not assessed as a risk factor, since the small number of non-white-British eyes in the study cohort made this inappropriate.

Presenting pre-operative IOPs (Table 5) were particularly high for eyes with secondary glaucoma (44 ± 12.5 mmHg; p<0.001), re-do surgery (34 ± 9.8 mmHg; p<0.001) and young patient eyes (34 ± 10.7 mmHg; p<0.001). Immediate pre-operative IOP was significantly higher for the eyes with secondary glaucoma (31 ± 10.2 mmHg; p<0.001) For all the risk factor sub-groups, the eyes were treated with more pre-operative topical therapy in comparison with the control group eyes (Table 5), especially for eyes with secondary glaucoma (3.1 vs. 1.4 agents; p<0.001).

	Control	≤55 years	Secondary Glaucoma	Previous surgery	Previous topical therapy	Re-do surgery	Trainee surgeon
n	67	43	40	90	211	66	66
Age years	72 ±6.7	47 ± 8.8***	60 ± 17.7***	76 ± 7.4***	70 ± 7.0	73 ± 10.2	71 ± 6.2
male:female %	45/55	56/44	45/55	39/61	45/55	42/58	47/53
Per-operative antifibrotic %	78	93*	80	94***	86	98***	87
5-FU:MMC	35:65	55:45	62:38	34:66	48:52	5:95	70:30
POAG	67	56	0	62	75	80	71
NTG %	27	2*	0	19	19	3**	11
Other	1	42**	100	15	5	17	18
Presenting highest IOP	26 ± 5.3	34 ± 10.7***	44 ± 12.5***	28 ± 6.5	28 ± 6.5*	34 ± 9.8***	30 ± 9.1**
Pre-op IOP	23 ± 5.1	25 ± 8.9	31 ± 10.2***	23 ± 5.3	22 ± 4.9	23 ± 5.5	23 ± 4.7
Pre-op Rx	1.4	2.2***	3.1***	2.3***	2.5***	2.6***	2.3***
Final IOP	12 ±4.2	12 ±3.9	13 ±5.3	12 ±5.1	11 ±3.3	11 ±3.3	13 ±3.9
Final Rx	0.3	0.6	0.4	0.2	0.3	0.5	0.6
% Drop from highest IOP	53%	61%*	68%***	56%	58%*	65%***	55%
% Drop from pre-op IOP	48%	47%	55%	48%	47%	50%	43%
Rx Change	-1.0	-1.6	-2.7***	-2.1***	-2.2***	-2.0***	-1.7**
Follow-up months	54 ± 31.9	77 ± 41.2**	64 ± 37.2	53 ± 31.5	66 ± 34.3	70 ± 32.7**	70 ± 32.7**

n: number of eyes; 5-FU: 5-fluorouracil; MMC: mitomycin-C; POAG: primary open angle glaucoma; NTG: normal tension glaucoma; IOP: intraocular pressure; Rx: mean number of topical anti-glaucoma medications. *p<0.05, **p<0.01, ***p<0.001

Table 5: Demography and IOP changes for the control and risk factor sub-groups.

The percentage drop in IOP from the presenting highest IOP was significantly greater for eyes with secondary glaucoma, those undergoing re-do trabeculectomy, of younger patients and those exposed to more than 3 years of topical medication (Table 5), but the percentage drops in IOP from immediate pre-operative IOP were similar for all sub-groups. With respect to trabeculectomy success rates, using the 3 criteria and 3 IOP thresholds the only statistically significant finding was a lower qualified (criterion 1) success rate for trainee surgeon cases at the ≤ 15 mmHg threshold (62% cf 70-85% for the other risk factor sub-groups; p<0.05). Two Kaplan-Meier survival curves for the risk factor sub-groups are shown in Figure 1. Figure 1 illustrates only the plots for (a) complete and (b) qualified success (criterion 1) at a threshold of ≤ 15 mmHg. There were no statistically significant differences between the survival results using any of the qualified success criteria, but for complete success, cases performed by trainees had shorter survival times.

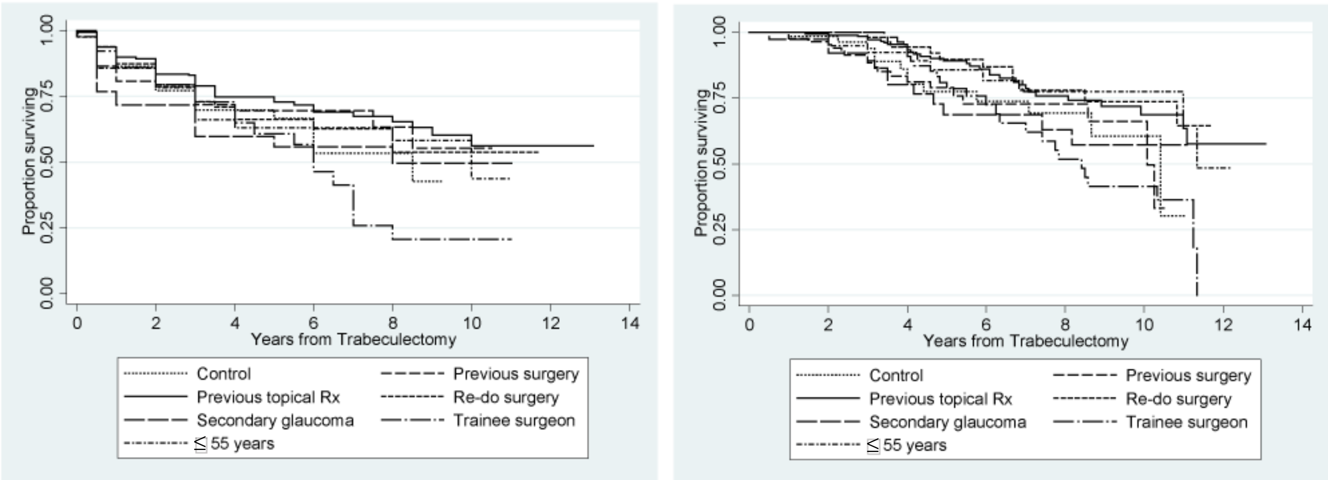

Figure 1: Kaplan-Meier survival curves for (a) complete and (b) qualified success (criterion 1) at a threshold of ≤15mmHg for the risk factor sub-groups (Rx=therapy).

In order to achieve success rates that were on a par with those of the control group more post-operative interventions were required for the risk factor sub-group eyes (Tables 6a and 6b). For all the risk factor sub-groups more eyes had releasable sutures pulled and when accounting for whether one or both were pulled, the rate of releasable suture removal was greater for all the risk factor sub-groups in comparison with the control eyes (Table 6a). The odds ratios for releasable suture removal were particularly high for the eyes that underwent re-do surgery (6.4) or previous surgery (5.6) and those that had surgery performed by trainee surgeons (5.7).

	Control	≤55 years	Secondary glaucoma	Previous surgery	Previous topical therapy	Re-do surgery	Trainee surgeon
Releasable pulled (% eyes of total)	13%	33%*	38%**	47%***	39%***	50%***	47%***
Releasable pulled (no./eye used)	1.6	1.7	1.7	1.7	1.6	1.8	1.4
Releasable rate (mean of total)	0.21	0.51*	0.60**	0.78***	0.62***	0.88***	0.65***
Odds Ratio	1.0	3.1*	3.9**	5.6***	4.2***	6.4***	5.7***
Bleb needling (% eyes of total)	19%	19%	30%	24%	16%	15%	29%
Bleb needling (no./eye needled)	2.2	1.8	1.4	1.5	1.8	1.3	2.1
Bleb needling rate (mean of total)	0.42	0.33	0.43	0.38	0.29	0.20*	0.61
Odds Ratio	1.0	0.95	1.78	1.34	0.80	0.74	1.7
*p<0.05, **p<0.01, ***p<0.001							

Table 6a: Post-operative interventions for the control and risk factor sub-groups.

More eyes with secondary glaucoma or those that had surgery performed by trainee surgeons required bleb needling procedures, although when accounting for the number of needling procedures performed per eye, the higher odds ratios (1.78 and 1.7 respectively) for bleb needling were not statistically significantly higher in comparison with the control group. Interestingly, the eyes that had undergone re-do trabeculectomy had a statistically significant lower bleb needling rate (0.2, p<0.05; OR 0.74).

Post-operative administration of either sub-conjunctival 5-FU or trans-conjunctival MMC was considered for both the early (3 months) and late post-operative periods (Table 6b). Antifibrotic administration was frequently performed as a prophylactic procedure at the time of routine cataract surgery in the eyes that had undergone previous trabeculectomy, so the assessment of late post-operative administration of antifibrotic was determined after censoring for such administration. In the early post-operative period, more eyes with secondary glaucoma required antifibrotic administration, but when accounting for the number of administrations per eye, the rate of antifibrotic administration in the first 3 post-operative months was significantly greater for all the risk factor sub-groups (Table 6b). For eyes with secondary glaucoma there was a 2.5 greater chance that early antifibrotic administration was needed (p<0.05). With respect to late post-operative administration of antifibrotic the rates for most risk factor sub-groups were less than for the control group. However, it was noted that one eye in the control group, that was particularly vascular in the late post-operative period underwent a disproportionately high number (10) of antifibrotic administrations. The outlier was removed from the final analysis (censoring for the administration of antifibrotic at the time of cataract surgery), which revealed that there was no statistically significant difference in the rate of late post-operative antifibrotic administration for any of the risk factor groups.

	Control	≤55 years	Secondary glaucoma	Previous surgery	Previous topical therapy	Re-do surgery	Trainee surgeon
Early antifibrotic (% eyes of total)	18%	28%	35%*	29%	25%	23%	32%
Early antifibrotic (no./eye treated)	1.9	2.0	1.6	2.0	1.9	1.9	1.8
Early antifibrotic rate (mean of total)	0.34	0.56***	0.58***	0.54***	0.49***	0.42***	0.58***
Odds Ratio	1.0	1.8	2.5*	1.9	1.5	1.3	2.1
Late antifibrotic (Phako surgery censored) (% eyes of total)	12%	10%	13%	8%	9%	11%	17%
Late antifibrotic (Phako surgery censored) (no./eye treated)	1.4	2.5	1.0	1.7	1.3	1.3	1.8
Late antifibrotic (Phako surgery censored) (mean of total)	0.20	0.25	0.16	0.13	0.12	0.13	0.44
Odds Ratio	1.0	0.81	1.11	0.63	0.70	0.93	1.47
*p<0.05, **p<0.01, ***p<0.001							

Table 6b: Early and late post-operative administration of either sub-conjunctival 5-fluorouracil or trans-conjunctival mitomycin-C for the control and risk factor sub-groups.

There were no major sub-group differences with respect to complications, the majority of which were minor and resolved. However, in comparison with the control group, eyes that underwent re-do trabeculectomy had more (17% cf 3%; p<0.01) complications at the time of surgery, the most significant complication being the discovery or evolution of a full thickness scleral defect requiring surgical repair in 5 cases. In comparison with the control group, complications identified one day after surgery were more common in eyes with secondary glaucoma (38% cf 18%; p<0.05) and in those that underwent re-do surgery (33% cf 18%; p<0.05), the most common of these being hyphaema. Early post-operative bleb leaks on day 1 were more common in trainee surgeon case eyes (17%) and at week 1 were more common in both trainee surgeon case eyes (23%) and younger patient eyes (21%), but the differences did not reach statistical significance. Overall early bleb leaks were 3.1 times more common in the trainee surgeon case eyes and 2.3 times more common in the younger patient eyes in comparison with the control eyes. The vast majority of bleb leaks resolved without intervention and although re-suture was 1.7 times more often required in trainee surgeon case eyes in comparison with control eyes (12% vs. 7%), this did not reach statistical significance.

In comparison with the control group, the trainee surgeon cases developed significantly more late complications (17% cf 3%; p<0.01), the most common of these being late bleb leaks, significant posterior synechiae formation, mega-blebs with dysaesthesia (resolved with bleb revision) and Tenon's capsule cysts (resolved with conservative management).

During the post-operative follow-up period there was an immediate early drop in recorded VA that in general returned to at or near to the pre-operative level by 3 months. Throughout the whole study period, eyes with secondary glaucoma had the lowest VA. During the late post-operative period there was a tendency for a slow decline in VA, although this was counteracted to some extent by cataract surgery in all risk factor sub-groups apart from for eyes that had undergone previous surgery or re-do trabeculectomy, where the majority of eyes were pseudophakic prior to undergoing trabeculectomy. The younger patient eyes underwent significantly less cataract surgery in comparison with the control group (17% vs. 43% of eyes; p<0.01), as did those cases with secondary glaucoma (22.5% vs. 43%; p<0.05), although this was not the case after adjusting for age. At the final post-operative visit, mean Snellen VA was either equal to, or a maximum of only one line worse for all of the sub-groups, in comparison with the pre-operative level.

Discussion

The success rate of trabeculectomy is very dependent on the definition of success that is utilized, the duration of follow-up and the population studied [27]. Thus, comparing results from different studies has to take multiple factors into account. For the eyes in the present study success was as high as 97% when using the qualified success criterion of IOP ≤ 21 mmHg, with or without the requirement of post-operative topical anti-glaucoma medication and/or bleb needling. However, for the same eyes, complete success (IOP ≤15 mmHg, no requirement for medication or needling) was significantly lower at 65%. However, a comparison with other reported success rates for large series of trabeculectomies (n>100) performed prior to the introduction of modern safe-technique surgery (with follow-up durations >2 years) [30-35], has shown that recent changes to the technique and post-operative management may have been successful in improving outcomes (Table 7); with the caveat that the precise definitions of success and the post-operative time point at which success has been calculated varies from study to study, being less strict for some and more strict for others [36]. In comparison with two recently published studies [35,36] and utilizing their criteria for success, the overall results for the present study were better, or similar when allowing for differing follow-up periods. Landers and co-workers reported a complete success rate of 57% in a study with maximum follow-up of 20 years (cf 69% for the present study, albeit with a shorter maximum follow-up period of 13 years) for achievement of ≤21 mmHg + ≥20% IOP reduction [35]. Jampel and co-workers reported complete success rates 4 years after surgery of 53% and 49% (cf 68% and 64% for the present study) for achievement of ≤18 mmHg + ≥20% IOP reduction and ≤15 mmHg + ≥25% IOP reduction, respectively [36]. It is important to note, however, that comparisons made between studies are flawed since patient populations differ and that the present study was only a single centre study.

Study	Eyes/Patients	Maximum follow-up duration (years)	Complete/Qualified success
Robinson et al. [30]	179/129	10	67%/86%
Ehmrooth et al. [31]	138/138	4	40%/52%
Diestelhorst et al. [32]	700/547	10	35%/44%
Molteno et al. [33]	289/193	15	-----/85%
Bevin et al. [34]	841/607	20	-----/79%
Landers et al. [35]	330/234	20	60%/90%
Jampel et al. [36]	797/634	9	53%/72%
Present study (≤ 21 mmHg)	636/507	13	71%/97%

Table 7: Complete and qualified success rates for long-term, large series trabeculectomies.

The main aim of the present study was to ascertain the effect of 'traditional' risk factors for filtration failure on the success of 'modern' trabeculectomy. Comparison between risk factor sub-groups was appropriate by use of the same surgical technique and same outcome criteria. Six 'traditional' risk factors for failure of trabeculectomy were considered in the present study. Relative youth (≤55 years of age), secondary glaucoma, previous intraocular surgery, chronic exposure to topical medication and re-do trabeculectomy were not identified as significant risk factors for failure of modern trabeculectomy. For most success criteria, results were less successful for trainee surgeons (with a greater risk of complications); this not being an unexpected finding and almost certainly relating to surgical technique, less experience (particularly with respect to suturing) and longer procedure duration, although this latter factor was not formally assessed. In contrast, cases carried out within the private healthcare system, where there was continuity of care from a single senior surgeon, were more successful. For the present study cases, the use of per-operative MMC was particularly important with respect to attaining complete success. In the UK the use of per-operative antifibrotics has increased dramatically from 6.4% (mainly 5-FU) in 1996 [37] to 93% (mainly MMC) in a series reported in 2013 [13]. The increased popularity of per-operative antifibrotics in the US preceded the UK and a survey of the American Glaucoma Society reported that MMC was used in 45% of primary trabeculectomies in 1996, this increasing to 68% by 2002

[38]. The reported dose and exposure times for MMC have varied considerably from 0.1 to 0.5 mg/ml and 15 seconds to 5 minutes respectively [37-43]. In the present study the vast majority of eyes were exposed to 5 minutes of 5-FU (25 mg/ml) or 3 minutes of MMC (0.2 mg/ml), this tending to be less exposure than in previous studies [37-43] despite the inclusion of patients with significant risk factors for failure, albeit that these latter cases were those where more MMC was utilised. It is possible that the relatively recent recommended change to use a wide posterior subconjunctival delivery of lower dose MMC for 2-3 minutes provides the optimal effect with minimal risk of adverse effects [9,10,13,44].

The relatively good results for eyes with 'traditional' risk factors for failure were not attained solely due to potentially improved surgical techniques or the per-operative use of antifibrotics such as MMC. It would appear that early post-operative procedures played a significant role in achieving longer-term success. In the UK the use of adjustable/releasable sutures has increased from 16.4% to >99% since 1996 [13,37]. In the present series, releasable sutures were placed in all cases and utilized post-operatively in 37% of cases. Compared with the control group, eyes with risk factors for failure required suture release 3.1 to 5.7 times more frequently. The highest rates of suture release were for eyes that had undergone previous surgery or those operated upon by trainee surgeons. It is important to appreciate that suture release is a simple, quick, relatively risk-free, procedure performed at the slit-lamp as an office procedure at the time of routine surgical follow-up [7,8]. It is the authors' opinion that the requirement for suture release should not, therefore, be considered as an adverse event, but more of an adjustment of the filtration rate made at an appropriate time point. In a recent multicentre analysis of UK trabeculectomy practice, post-operative suture manipulation (adjustment or release) was performed in 43% of cases of primary trabeculectomy performed on eyes with open angle glaucoma [13]. The use of adjustable/releasable sutures not only provides the opportunity for improving filtration flow rates, but also has the aim of reducing the risk of early post-operative hypotony [7,8,29,45]. In the present series only 5% of eyes developed early hypotony maculopathy which was temporary in all but one eye.

In contrast to suture manipulation, bleb needling is a more invasive procedure with inherent, although rare, risks [46,47]. In the present study bleb needling performed within the first 3 post-operative months was not considered a reason to define the trabeculectomy as failed, but unlike in some studies, eyes requiring a needling after 3 months were considered as failures. Failed trabeculectomy function can frequently be revived even following 'failure' after many years of follow-up and for this reason it was considered inappropriate to include such eyes in an assessment of the management of eyes with known risk factors for failure. For the present study patient cohort the rate of post-operative bleb needling was little different between all the risk factor sub-groups. Interestingly, the eyes undergoing re-do trabeculectomy required less post-operative bleb needling compared to the other groups, potentially due to the exposure to more per-operative antifibrotic (especially MMC), a reflection of the pre-operative perceived high risk of failure that re-do surgery carries [48,49]. Although more eyes with secondary glaucoma required post-operative bleb needling, the actual rate of bleb needling was no different to that for the control group.

In the present study per-operative complications were rare, affecting less than 7% of eyes. The most common per-operative complications were conjunctival tears requiring additional suturing during the procedure (2%) and subconjunctival haemorrhage (1.7%), but it is important to note that in one case there was a significant choroidal haemorrhage resulting in visual loss. Per-operative complications were more common in eyes undergoing re-do surgery, as might be expected when operating on eyes with disturbed anatomy. Early post-operative complications in the present study were less frequent in comparison with those reported in the UK national survey of trabeculectomies performed in the early to mid-1990s [50]. Hyphaema occurred in 13.4% (cf 24.6%), bleb leak in 13.2% (cf 17.6%), choroidal effusion in 11.9% (cf 14.1%) and shallow a/c in only 9.4% (cf 23.9%) of cases. The authors believe that the use of tight releasable sutures in the present series of trabeculectomies was the most likely reason for the reduced occurrence of shallow a/c in the early post-operative period. As might be expected, early post-operative complications were more common in eyes undergoing re-do surgery, with secondary glaucoma and those operated upon by trainee surgeons. In addition, younger patients appeared to be more susceptible to early post-operative bleb leaks, but a reason for this was not identified and the tendency failed to reach statistical significance (as with the trainee surgeon cases). Again it is important to note that overall, early post-operative complications of high clinical significance did occur in 9 eyes (1.4%), this including 2 cases of choroidal haemorrhage and 2 cases of malignant glaucoma. The single case of wipe-out was almost certainly related to pre-operative disease severity and occurred 3 years after successful trabeculectomy (Table 4b). Late post-operative complications were more common in eyes operated upon by trainee surgeons, but overall were rare. Of particular importance there were no cases of endophthalmitis identified during the mean follow-up period of over 5 years.

In conclusion, modern technique trabeculectomy had a high success rate and together with modern post-operative management eyes with 'traditional' risk factors for failure achieved high success rates. Trabeculectomies performed by trainee surgeons tended to be less effective, with more complications, compared with those performed by a senior surgeon. The factors of major importance with respect to success in eyes with higher risk of failure appeared to be the use of MMC (or 5-FU), releasable sutures and bleb needling (for qualified success criteria). Other potential factors of importance include the risk stratification itself, training, experience, continuity of care and the use of post-op steroid, but these factors were not assessed.

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