LONG-TERM RESULTS AND COMPLICATIONS AFTER TRABECULECTOMY WITH A SINGLE PER-OPERATIVE APPLICATION OF 5-FLUOROURACIL

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SUMMARY

We retrospectively evaluated a consecutive series of 45 patients (45 eyes) who underwent trabeculectomy augmented with a single intra-operative 5 minute application of 5-fluorouracil (5-FU; 25 mg/ml). All patients were at an increased risk of subconjunctival fibrosis and surgical failure. The mean follow-up period was 24 months (range 12–42, SD 6.9). The mean pre-operative intraocular pressure (IOP) was 29.1 mmHg (SD 6.1) and the mean IOP at the last post-operative visit was 16.6 mmHg (SD 6.4) ($p < 0.0001$) with a mean IOP reduction of 42%. The number of medications reduced from a mean of 2.3 (SD 0.7) pre-operatively, to 0.8 (SD 0.7) post-operatively ($p < 0.0001$) and 22 eyes (49%) required no topical treatment for IOP control. An IOP of 21 mmHg or less with or without medications was achieved in 80% of cases. There was no significant difference in final IOP or success rate over time between low- and high-risk patients, although the low-risk patients did better in the first 12–18 months. Complications included hypotony maculopathy in 2 cases (4%), leaking bleb in 5 cases (11%) and giant bleb in 1 case (2%), giving a total of 8 cases (18%) with bleb-related sequelae. In the short to medium term, a single per-operative application of 5-FU is a useful adjunctive treatment during glaucoma filtering surgery for low- to moderate-risk cases, although a steady increase in the failure rate was associated with increasing length of follow-up.

The most common cause of failure of glaucoma filtering surgery is the formation of excessive scar tissue beneath the conjunctiva, which occurs as a natural healing response to surgical trauma.[1] This response is exaggerated in cases of previous ocular surgery, aphakia or uveitis, and also where the patient is of a young age or of African or Asian race. Locally derived fibroblasts are thought to be the principal cellular component responsible for this reaction,[1] and laboratory studies have shown that proliferation of these cells can be modified via the use of chemotherapeutic agents such as 5-fluorouracil (5-FU) and mitomycin C (MMC).[2–4]

Fluorouracil, a pyrimidine analogue, is an anti-neoplastic agent which interferes with normal cell mitosis by competitively inhibiting the enzyme thymidilate synthetase and therefore the synthesis of DNA and RNA.[5] 5-FU, when given by subconjunctival injection in the post-operative period, has been shown to increase the success rate of glaucoma filtering surgery in high-risk patients.[6–9] Likewise, success rates are improved following the use of MMC applied intraoperatively.[10–14] However, MMC has a more profound inhibitory effect on subconjunctival fibroblasts than 5-FU[15] and such filtering blebs tend to be extremely thin and avascular with the attendant risks of hypotony maculopathy[10,16] and bleb-related endophthalmitis.[17]

Administered post-operatively, 5-FU has several disadvantages, not least the need for repeated subconjunctival injections, which can be painful and inconvenient to the patient, and also an associated higher risk of corneal complications.[18] More recently there has been a trend towards using 5-FU as a single exposure given at the time of surgery, largely based on the results of laboratory studies which suggested that a single intraoperative application would be as effective as repeated subconjunctival injections in inhibiting fibroblast proliferation.[2,3] Recent clinical studies with limited follow-up (range 3–12 months) supported these findings, with success rates between 83% and 91%.[19–21] Mora *et al.*[22] in a large study of 140 eyes with a mean follow-up of 16 months have

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also shown an impressive success rate (< 21 mmHg, allowing medications) of 92%, with 72% having an IOP < 15 mmHg (and > 30% drop in IOP) at the last follow-up. However, in this study 56% of eyes had no increased risk of subconjunctival fibrosis. This retrospective study was undertaken to evaluate the long-term efficacy and complications of intraoperative sponge 5-FU application in a group largely consisting of high-risk patients.

PATIENTS AND METHODS

A consecutive series of 45 eyes in 45 patients undergoing glaucoma filtration surgery with adjunctive 5-FU was studied. There were 25 men and 20 women, all of whom were Caucasian apart from 4 women and 1 man of Asian origin. The mean age was 53.0 years (range 19–78, SD 15.8) and the mean follow-up period was 24 months (range 12–42, SD 6.9). Pre- and post-operative examination included visual acuity, IOP measurement by Goldmann applanation tonometry, slit lamp biomicroscopy and optic disc assessment using a +90 dioptre or +78 dioptre Volk lens. The pre-operative IOP was taken as the mean value of the last three recordings prior to surgery; the post-operative IOP was the value at the last follow-up visit. Visual field perimetry was performed at approximately yearly intervals post-operatively, using threshold (Humphrey, 24-2 program) and supra-threshold (Medmont, Goldmann and Friedmann) analysers.

Surgery was performed on the basis of an uncontrolled IOP despite maximally tolerated medical therapy. Two eyes with a pre-operative IOP of 21 mmHg and 19 mmHg were showing progressive optic nerve damage. There was a total of 5 surgeons (3 consultants and 2 senior registrars) who used a standardised surgical technique which included a limbal-based conjunctival flap with or without excision of Tenon's capsule. A small surgical sponge (Sugi Steril, John Weiss) was trimmed and soaked in 5-FU 25 mg/ml (David Bull Laboratories, Warwick, UK) and then applied to the sclera which was covered with conjunctiva, taking care to try to avoid contact between the cut conjunctival edge and the sponge. The sponge was left in place for 5 minutes and was replenished with 1 or 2 drops of 5-FU every minute using an insulin syringe and a 25 gauge needle. Following this the sclera was thoroughly irrigated with 20 ml normal saline. A one-third to one-half thickness rectangular scleral flap measuring 4 mm × 3 mm was then dissected into clear cornea and a block of corneoscleral tissue measuring 3 mm × 1 mm was excised followed by a peripheral iridectomy. The scleral flap was sutured with two 10/0 monofilament nylon sutures and the conjunctiva was closed with interrupted 10/0 monofilament nylon or continuous 8/0 vicryl sutures.

Post-operative medications included topical dexamethasone 0.1% applied 6–8 times daily and chloramphenicol eye drops 4 times a day. Topical steroids were tailed off slowly over a period of 3 months. Post-operative examinations and measurements were made at 1 day, 1 week, 1 month, 3 months, 6 months and then 6 monthly, or between these times if the clinical situation demanded. Laser suture lysis was performed within the first 2 weeks depending on the IOP and the appearance of the bleb.[23] Additional subconjunctival 5-FU injections (2.5 mg via a 30-gauge needle into the bleb) were given if there were signs of bleb failure within the first 21 post-operative days. The criteria for surgical outcome were defined as follows:

Complete surgical success: an IOP of 21 mmHg or less without any anti-glaucoma medication.
Qualified success: an IOP of 21 mmHg or less with anti-glaucoma treatment.
Unqualified success: an IOP of 21 mmHg or less regardless of anti-glaucoma treatment.
IOP of less than 15 mmHg and > 30% drop in IOP:[22] regardless of anti-glaucoma treatment.
Failure: an IOP of 21 mmHg or greater regardless of anti-glaucoma treatment.

For the analysis of results the patients were separated into high-risk and low-risk groups. High-risk factors included previous failed filtration surgery, uveitis, pseudophakia or aphakia or neovascularisation.[18,24–26] Low-risk factors included age under 45 years, African or Asian race or previous topical medications for over 3 years.[27–31]

A Wilcoxon matched-pairs signed-rank test was used to evaluate the intra-individual changes in IOP and the pre-operative to post-operative change in anti-glaucoma medications. A Kaplan–Meier analysis was performed to assess how success changed over 6 monthly intervals using three criteria: complete success, unqualified success and IOP<15 mmHg. A comparison of the survival curves between the low- and high-risk groups for the three success criteria was undertaken using the log rank test. In addition any pre-operative to post-operative change in optic disc cupping and visual field loss was documented.

RESULTS

Patient details, including causes of glaucoma and risk factors for surgical failure, are summarised in Table I. Thirty-five patients were at high risk of subconjunctival fibrosis and therefore surgical failure, with many patients having more than one risk factor. There were 10 cases which were in the low-risk category.

Fig. 1 shows a scatter plot of the pre- and post-operative IOPs. The mean pre-operative IOP was

Table I. Patient details

Patient no.	Age (years)	Sex	Eye	Follow-up (months)	IOP (mmHg)		Medications		Visual acuity		Diagnosis	Risk factors	Outcome
					Pre-op.	Final	Pre-op.	At last visit	Pre-op.	Last			
1	59	F	L	42	36	22	3	1	6/9	6/6	POAG	Race	Failure
2	54	F	R	39	28	24	2	1	6/5	6/5	POAG	Race	Failure
3	42	M	R	33	48	10	3	1	6/60	6/60	Uveitic glaucoma	Young age, uveitis, pseudophakic, failed trab.	Qualified success
4	44	M	L	32	42	16	2	3	6/60	6/36	Uveitic glaucoma	Young age, uveitis, pseudophakic, failed trab.	Qualified success
5	38	M	L	32	26	16	2	0	6/12	6/12	POAG	Young age	Complete success
6	36	F	L	30	23	17	2	1	CF	CF	Secondary glaucoma	Young age, PK ×2 (*Acanthamoeba*), pseudophakic, failed trab. + Molteno	Qualified success
7	19	M	R	31	33	30	3	3	6/12	6/60	Uveitic glaucoma	Young age, uveitis, pseudophakic, failed trab.	Failure
8	63	F	R	28	32	16	1	1	6/24	6/12	CACG	Failed iridocleisis	Qualified success
9	72	M	R	33	23	7	1	0	6/9	6/9	POAG	Failed trab.	Complete success
10	72	M	R	30	27	15	2	0	6/9	6/18	POAG	Failed trab., previous ALT	Complete success
11	65	M	L	30	37	12	2	1	6/36	6/60	Rubeotic glaucoma	Rubeosis	Qualified success
12	36	M	R	33	26	24	3	2	6/5	6/6	Pigmentary glaucoma	Young age	Failure
13	40	M	L	27	39	16	2	1	6/60	6/60	Uveitic glaucoma	Young age, uveitis, pseudophakia	Qualified success
14	65	F	L	30	28	16	2	2	6/9	CF	POAG	Race, pseudophakia	Qualified success
15	39	M	R	26	28	12	2	0	6/12	6/12	POAG	Young age	Complete success
16	32	M	L	30	23	10	3	1	6/6	6/6	Uveitic glaucoma	Young age, uveitis	Qualified success
17	52	F	L	23	19	17	3	1	6/6	6/5	POAG	Failed trab. ×3, failed Molteno	Qualified success
18	28	F	R	26	35	37	2	3	6/9	6/12	Uveitic glaucoma	Young age, uveitis, aphakic	Failure
19	19	M	R	24	34	30	3	3	2/60	2/60	Aphakic glaucoma	Young age, aphakic, failed trab. ×3, failed Molteno	Failure
20	71	F	L	24	26	12	3	1	6/24	6/24	POAG	Failed trab. ×2, previous ALT	Qualified success
21	52	F	R	20	21	18	2	0	6/36	6/36	POAG	Failed trab.	Complete success
22	43	F	L	21	26	18	2	0	6/36	6/60	Uveitic glaucoma	Young age, uveitis	Complete success
23	78	F	R	24	25	27	3	2	6/60	1/60	POAG	Failed trab.	Failure
24	52	F	L	20	32	17	3	0	6/9	6/9	CACG	Pseudophakia, failed trab.	Complete success
25	66	M	R	19	24	14	2	0	6/6	6/9	POAG	Pseudophakia	Complete success
26	63	F	R	18	29	14	3	0	6/18	6/18	POAG	Race	Complete success
27	44	M	L	20	26	10	1	0	6/24	6/24	Pigmentary glaucoma	Young age	Complete success
28	39	F	L	20	30	23	3	3	CF	HM	Aniridia	Aniridia, pseudophakia, PK ×3	Failure
29	36	M	R	24	27	28	3	1	1/60	PL	Aphakic glaucoma	Young age, failed trab. ×3, aphakic	Failure
30	61	F	R	18	32	10	2	0	6/5	6/9	CACG	Previous PI, failed trab.	Complete success
31	48	M	R	20	25	17	2	0	6/5	6/5	Pigmentary glaucoma	Race	Complete success
32	67	M	R	19	29	16	2	0	6/6	6/9	POAG	Failed trab., pseudophakic, previous ALT	Complete success
33	65	F	L	18	23	14	2	0	6/12	6/12	POAG	Failed trab., previous ALT	Complete success
34	34	M	L	18	32	16	2	0	3/36	3/36	ICE syndrome	ICE, young age	Complete success
35	72	M	L	14	28	15	2	2	1/60	1/60	POAG	Proliferative diabetic retinopathy	Qualified success
36	72	M	R	26	32	8	3	0	6/9	6/9	POAG	Failed trab.	Complete success
37	44	M	R	18	23	12	1	0	6/6	6/4	Pigmentary glaucoma	Young age	Complete success
38	50	M	L	19	26	14	3	0	6/18	6/9	Uveitic glaucoma	Uveitis, failed trab. ×2	Complete success
39	53	M	R	19	41	15	3	1	6/12	6/9	Uveitic glaucoma	Uveitis, failed trab. ×2, pseudophakia	Qualified success
40	67	F	L	12	26	9	2	0	6/9	6/12	POAG	Failed trab.	Complete success
41	74	M	L	14	34	18	3	1	6/24	6/9	Uveitic glaucoma	Uveitis, failed trab.	Qualified success
42	78	F	R	18	31	13	1	1	6/9	6/6	POAG	Failed trab. ×3, pseudophakia	Qualified success
43	48	F	L	26	20	10	3	0	6/24	6/36	POAG	Failed trab. ×3	Complete success
44	70	M	L	12	31	15	2	0	6/60	6/60	CACG	Failed trab., pseudophakia	Complete success
45	63	F	L	20	25	16	3	0	6/6	6/6	POAG	Drops for 10 years	Complete success

POAG, primary open angle glaucoma; CACG, chronic angle closure glaucoma; ICE, irido-corneal endothelial syndrome; PK, penetrating keratoplasty; ALT; argon laser trabeculoplasty; trab., trabeculectomy.

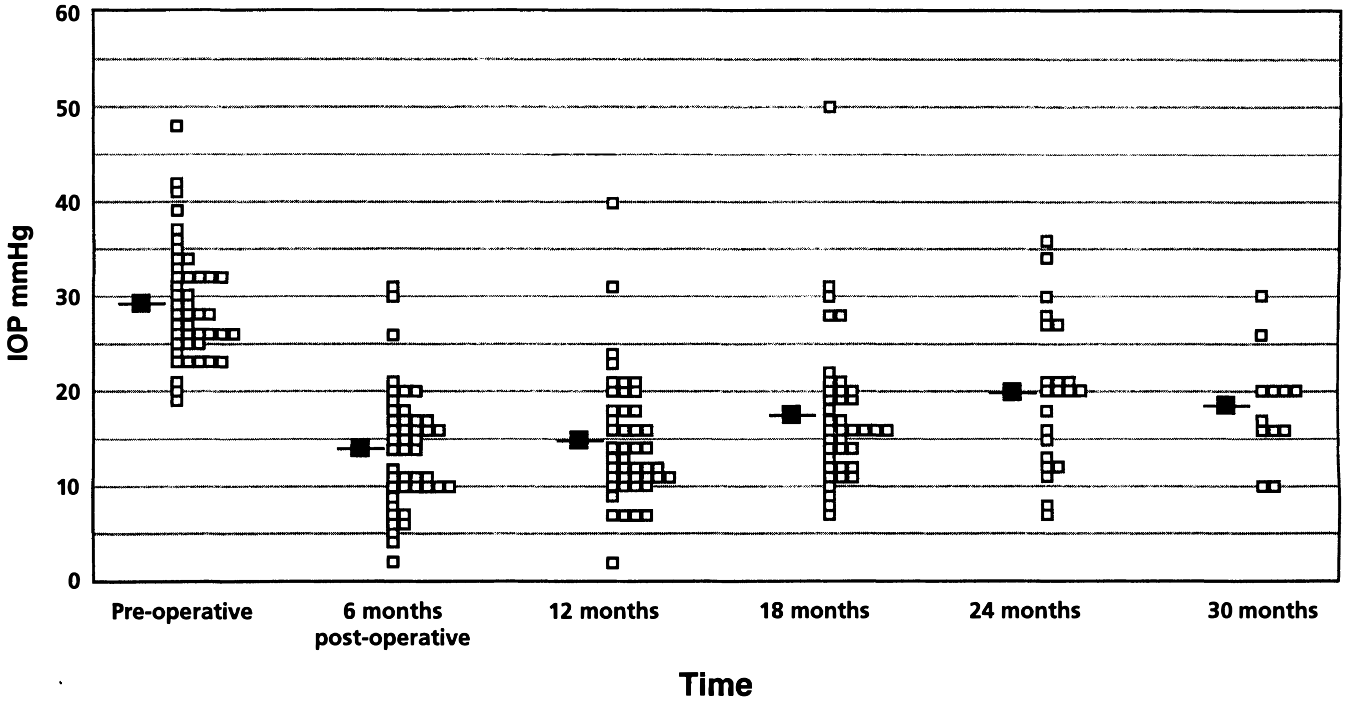

Fig. 1. *Scatterplot of intraocular pressures (IOPs) pre- and post-operatively. The filled squares indicate the mean IOP values.*

29.1 mmHg (range 19–48, SD 6.1) and the mean post-operative IOP at the last follow-up was 16.6 mmHg (range 7–37, SD 6.4) ($p < 0.0001$). Complete success was achieved in 22 eyes (49%) and qualified success in 14 eyes (31%), giving an unqualified success rate of 80%. Nine eyes (20%) have failed, 6 of which were in the high-risk group and 3 in the low-risk group (Table I). One of these underwent a further 5-FU trabeculectomy at the time of last follow-up. The mean number of medications pre-operatively was 2.3 (SD 0.7) reducing to 0.8 (SD 0.7) post-operatively ($p < 0.0001$). Twenty-three patients (51%) required topical treatment at the last follow-up, 20 of whom were in the high-risk group and 3 in the low-risk group. Table II illustrates the IOP reduction for the different risk groups and the group as a whole, and also the success rates for the three different criteria at the time of last follow-up.

The Kaplan–Meier survival curve for trabeculectomy with per-operative sponge 5-FU is shown in Fig. 2. Survival varies according to the criteria used to define success. Fig. 3 compares the survival curves between low-risk and high-risk eyes for the three different success criteria. There was no significant difference in the survival curves between the two groups (complete success, log rank 1.38; unqualified success, log rank 0.24; IOP < 15 mmHg and > 30% reduction in IOP, log rank 0.09; significance ≥ 2.0).

Argon laser suture lysis was performed to augment bleb formation in the early post-operative period in 4 eyes. Six eyes in the high-risk group showing evidence of early bleb failure required post-operative subconjunctival injections of 5-FU. The number of injections ranged between two and five. Of those eyes that required post-operative subconjunctival 5-FU, 1 eye failed at 4 months, 2 eyes failed at 18 months and the remaining 2 eyes remain controlled on a topical β-blocker alone.

Table II. Intraocular pressure, intraocular pressure reduction and success rates within groups at the final follow-up

	High risk (n = 35)	Low risk (n = 10)	Total (n = 45)
IOP (mean ± SD)	16.5 ± 6.7	16.7 ± 5.1	16.6 ± 6.4
IOP reduction (%) (mean ± SD)	42.5 ± 23.4	38.8 ± 17.4	41.7 ± 22.1
Complete success (%)	43 (n = 15)	70 (n = 7)	49 (n = 22)
Unqualified success (%)	83 (n = 29)	70 (n = 7)	80 (n = 36)
IOP <15 and >30% reduction (%)	49 (n = 17)	40 (n = 4)	47 (n = 21)

IOP, intraocular pressure (mmHg).

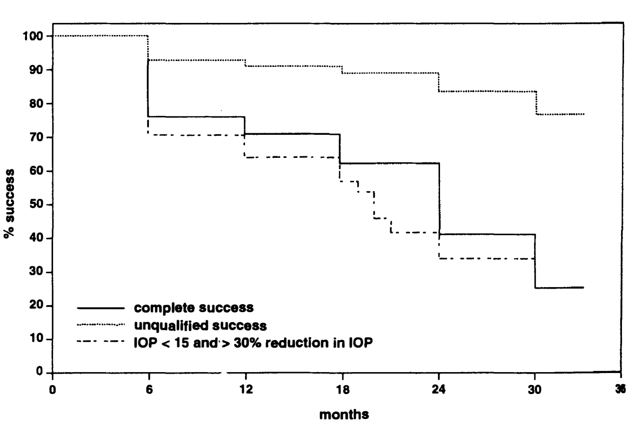

Fig. 2. *Kaplan–Meier survival analysis of trabeculectomy with per-operative sponge 5-fluorouracil.*

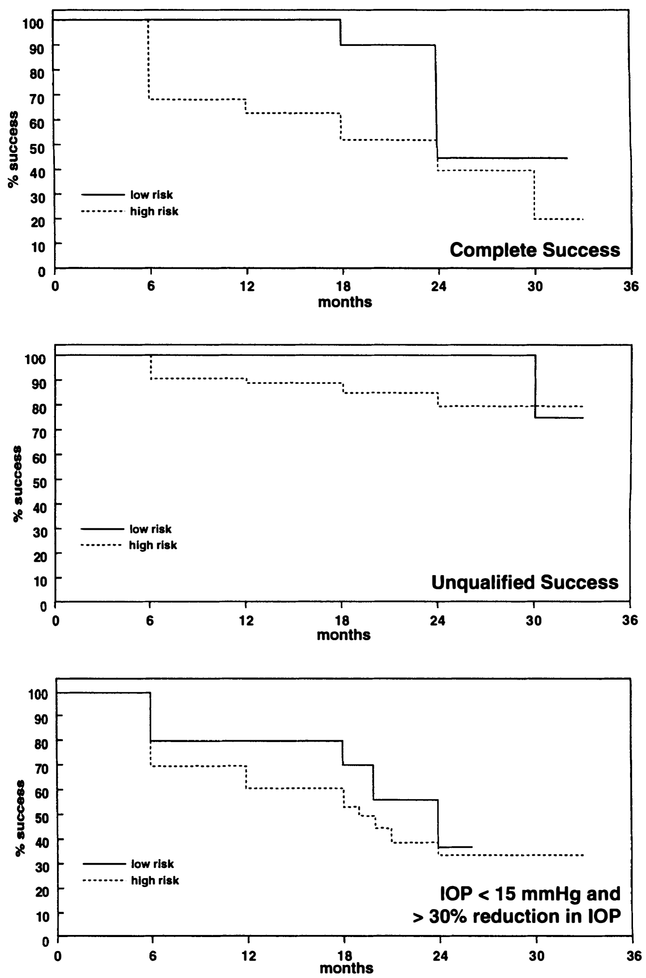

Fig. 3. *A comparison of the Kaplan–Meier survival curves between the high- and low-risk groups according to the different success criteria.*

Visual field tests were performed in 30 of 45 patients (67%). Perimetry was not performed in those patients whose visual acuity was too poor for meaningful field assessment. The types of perimeter used were as follows: Medmont, 14 cases; Humphrey (24-2 program), 6; Goldmann, 5; Friedmann, 5. Only 2 patients showed evidence of deterioration in the visual fields. The first was a 72-year-old man with primary open angle glaucoma (POAG) who demonstrated progression of superior and inferior arcuate scotomas 2 years post-operatively in the presence of good IOP control. The IOP at 2 years was 8 mmHg and did not rise above 14 mmHg throughout follow-up. The second patient was a 78-year-old woman with POAG who also demonstrated progression of upper and lower arcuate scotomas at the 12 month follow-up visit in the presence of an IOP below 15 mmHg. One patient showed documented evidence of progression of glaucomatous disc damage following surgery. This was a 19-year-old man with severe uveitic glaucoma and poor IOP control whose optic disc cupping over a 2½ year period deteriorated from a cup-to-disc ratio of 0.9 to an end-stage cup in the presence of a reduction in visual acuity from 6/12 to 6/60.

Table III summarises the complications encountered. There were no serious bleb-related or corneal complications amongst those patients requiring post-operative subconjunctival injections of 5-FU. Hypotony maculopathy was seen in 2 eyes, 1 of which settled spontaneously 2 weeks post-operatively. The second case required four surgical procedures to revise the bleb, the last of which was combined with a phacoemulsification with foldable intraocular lens implant through a separate clear corneal incision. The IOP at the last follow-up was 11 mmHg on no topical medication with a visual acuity of 6/6. There was 1 case of leaking bleb 5 days post-operatively which settled spontaneously after 6 days, and 1 case of persistent corneal epithelial defect which lasted for 1 year. This, however, was in a patient who had had a previous corneal graft for *Acanthamoeba* keratitis.

Amongst the late complications there was 1 case of delayed epithelial defect occurring 3 months post-operatively which settled after 6 weeks. There were 4 cases of leaking bleb, 1 at 1 year which resolved spontaneously, another which required refashioning of the conjunctiva 9 months post-operatively and 2 which were described as transconjunctival pinpoint leaks which were observed. About half the blebs (49%) were described as cystic, 1 of which was a giant bleb overhanging the cornea (initially a Tenon's cyst) which did not require surgical revision. There were no cases of bleb-related endophthalmitis. Retinal detachment occurred in 2 eyes: an aphakic eye in which there was vitreous loss at the time of trabeculectomy and a myopic pseudophakic eye.

Cataract occurred in 4 cases, 1 of which was progression of pre-existing lens opacities; 3 of these cases underwent successful phacoemulsification with lens implantation. At the last follow-up, visual acuity

Table III. Intraoperative, early and late post-operative complications

Intraoperative	
Vitreous loss	1 (2%)
Early (within 2 months)	
Hyphaema	11 (24%)
Encysted bleb	9 (20%)
Choroidal detachment	6 (13%)
Subconjunctival 5-FU	6 (13%)
Hypotony maculopathy	2 (4%)
Anterior uveitis	2 (4%)
Flat anterior chamber (re-formed)	2 (4%)
Bleb leak	1 (2%)
Epithelial defect	1 (2%)
Revision of trabeculectomy	1 (2%)
Late	
Cystic bleb	22 (49%)
Giant bleb	1 (2%)
Leaking bleb	4 (9%)
Cataract	4 (9%)
Refashioning of bleb	2 (4%)
Retinal detachment	2 (4%)
Epithelial defect	1 (2%)

was within 1 line or better than pre-operative levels in 41 of 45 eyes (Table I). Of the 4 cases with a deterioration in visual acuity, there were 2 retinal detachments (6/9 to CF, and CF to PL), 1 posterior subcapsular cataract (6/9 to 6/18) that has not yet required surgery and 1 case of chronic uveitis with progression of glaucoma (6/12 to 6/60).

DISCUSSION

Blumenkratz was the first to use 5-FU in ophthalmology in 1982 for the treatment of experimental vitreoretinopathy. It has since gained wide acceptance as a useful antiproliferative agent in glaucoma surgery. Initially applied as a series of post-operative injections, it was not until the early 1990s that the per-operative application of 5-FU on a sponge was first suggested. The rationale was that by applying the drug directly to the sclera, only the target tissues would be exposed to maximal drug concentration, and thereby the incidence of 5-FU related complications would be expected to be reduced.

The unqualified success rate (IOP < 21 mmHg with or without medications) of 80% in this group of largely high-risk patients compares favourably with the pilot study of Lanigan *et al.*[19] (91% unqualified success rate) where the maximum follow-up was only 9 months. Traditionally the arbitrary figure of 20 or 21 mmHg has been used as the target pressure by which success is defined, but it is now recognised that lower IOPs (i.e. in the low teens) are considered to be desirable for optic nerves already damaged by glaucoma. The third criterion for outcome, i.e. an IOP < 15 mmHg and > 30% reduction, as used by Mora *et al.*,[22] therefore provides the most realistic assessment of the value of per-operative 5-FU in high-risk patients. Table II demonstrates that at last follow-up, this goal is being achieved in only 47% of eyes (n = 21), one third of which (n = 7) required topical medication. If those patients requiring topical medication are excluded, then by the strictest definition of outcome (IOP < 15 mmHg and > 30% reduction, without medication) the success rate falls to 31% (n = 14).

The Kaplan–Meier curve (Fig. 2) shows that at 33 months post-operatively, using the most lenient criterion, the success rate is maintained at 77%. However, if the more stringent criteria are applied there is a steady drop-out as more eyes fail to survive, until at 33 months only 25% are maintaining an IOP < 15 mmHg and > 30% reduction. It would appear, therefore, that the longer the post-operative period, the greater the failure rate, and over the longer term the ability to maintain a low IOP amongst a high number of patients is disappointing. The Kaplan–Meier statistics do, however, become less reliable as the post-operative interval increases, due to the fact that the success rates are calculated from fewer patients and therefore any failures produce a much greater proportional loss of survival. It is interesting to note that there was no significant difference in the long-term survival between the low-risk and high-risk groups, although the low-risk group tended to fare better within the first 12–18 months. It should also be noted that the number in the low-risk group was small ($n = 10$), making comparison less meaningful.

Comparison with the study of Mora *et al.*[22] is difficult because approximately half the patients in that study had no increased risk for surgical failure. If these 'low-risk' patients are excluded, they would still appear to have slightly more favourable results, with 90% achieving an IOP < 21 mmHg (allowing medications) and 62% achieving an IOP < 15 mmHg with > 30% drop in IOP (allowing medications). It should be noted, however, that the follow-up period in this study was shorter than in our study (mean 16 months, range 2–42) where the minimum follow-up was 12 months; the concentration of 5-FU used was 50 mg/ml compared with 25 mg/ml in the current study; and 29% of their patients had a pre-operative IOP of less than 21 mmHg. Accurate comparison is also hampered by the variation in risk profile of the different patient groups. For example, all high-risk patients were included in the current 5-FU study whereas in the study by Mora *et al.* some of the very high-risk patients were assigned to MMC trabeculectomy and therefore not represented in their results.

By way of comparison with intraoperative sponge MMC for high-risk patients, there is a lack of published data examining the success in achieving IOPs in the low teens, even in the short term. Skuta *et al.*[14] found that in 20 eyes, 60% achieved an IOP of 12 mmHg or less at 6 months, and 74% were medication free. These figures are comparable with those of Mora *et al.*[22] using sponge 5-FU (62% IOP < 15 mmHg with > 30% reduction, 70% medication free) and would appear to be superior to the results of this study (47% IOP < 15 mmHg and > 30% reduction, 49% medication free) bearing in mind the short length of follow-up. At the 6 month follow-up visit in this study our equivalent figures are 71% IOP < 15 mmHg (and > 30% reduction) with 76% medication free.

Although the primary endpoint of the study was IOP control rather than preservation of visual function, visual acuity and visual field data were analysed, accepting the limitations of recording data in a retrospective study. Computerised automated perimetry has done much to improve the assessment of a patient's visual status, although a simple, accurate and economically viable method of both high specificity and sensitivity for early detection of significant change in an individual's visual field has yet to be developed. In view of these problems, control of IOP has traditionally been used as the main criterion for success. Measurement of IOP is easy, accurate, reproducible and objective, and provides data that are easily analysed statistically. The term 'success' is therefore synonymous with surgical success rather than disease control, although a lower IOP cut-off level is likely to bring pressure control in line with disease control.

The fact that 33% ($n = 15$) of patients were unable to perform a useful field test reflects an advanced state of visual impairment. This high degree of pre-operative damage reduces the ability to detect a treatment effect. Despite this, visual acuity was well maintained (within 1 Snellen line or better) in 91% ($n = 41$) of patients and only 2 of the 30 patients who performed perimetry demonstrated progression of arcuate scotomas at 12 and 24 months post-operatively, both of whom maintained IOPs at or below 15 mmHg. Clinical estimation of progression of glaucomatous optic disc cupping is even less reliable in a retrospective case note analysis when one is reliant on the subjective assessment of cup-to-disc ratios (CDR) and the variable artistic skills of a number of different doctors, rather than serial optic disc photographs. There was nevertheless documented progression of optic disc cupping (CDR 0.9 to 1.0) in only 1 case, this being in a 19-year-old man with severe uveitic glaucoma and poorly controlled IOP whose visual acuity dropped from 6/12 to 6/60 over 2½ years of follow-up.

There was a low rate of corneal complications, with only 2 eyes (4%) developing epithelial defects. Corneal epithelial cells are particularly susceptible to the effects of 5-FU, and the incidence of corneal-related problems appears to be much greater with the use of subconjunctival injections, rates varying between 29% and 64% depending on the dose of 5-FU used.[18,32] This could be attributable to the fact that 5-FU applied per-operatively remains relatively localised to the area of application and is then rapidly washed away during irrigation. Thorough irrigation following application of the sponge minimises the risk of 5-FU entering the anterior chamber when creating the ostium, thus avoiding toxicity to the corneal endothelium,[33] the lens[33] and the ciliary body. In contrast, following a subconjunctival injection, 5-FU can leach out of the puncture site into the pre-corneal tear film, thereby remaining in contact with the corneal epithelium for several hours.

Late bleb leaks were detected in 4 eyes (9%), in addition to 1 case occurring within the first week. By taking care to avoid contact between the cut conjunctival wound edge and the sponge, and by meticulous suturing of the conjunctiva, the incidence of wound dehiscence and wound leaks in the early post-operative period can be minimised. Antimetabolite administration *per se* does not cause a wound leak in the early post-operative period, since the wound should be held watertight by the suture regardless of the degree of healing; however, it will unmask an inadequately closed wound. The incidence of bleb leak in this study was considerably lower than the 25–35% reported by other studies using post-operative injections.[18,34] Ocular hypotony associated with maculopathy was seen in 2 patients (4%) in the early post-operative period. In 1 case this persisted for many months and required several surgical revisions to the bleb before a successful outcome in terms of visual recovery (6/6) and IOP control (11 mmHg) was achieved. Prata *et al.*[35] found hypotonous maculopathy in 4.1% of all their MMC-treated eyes compared with an incidence of 1.3% in eyes treated with post-operative 5-FU. Long-term hypotony is a potentially serious complication[34,36,37] and permanent visual impairment may result from chronic macular changes. Young myopic eyes appear to be most at risk, perhaps due to low scleral rigidity.[37] Giant bleb, which overhangs the cornea, is another long-term bleb-related complication which often gives rise to a persistent foreign body sensation and ocular surface disturbance. The single case encountered in this series did not require surgical excision.[36]

Late bleb-related endophthalmitis is a potentially devastating complication which has been reported following the use of 5-FU given post-operatively, at rates varying between 1.9% and 9.4%.[7,34,36,38] These are high rates for such a severe complication and it is interesting to note the higher figure of 9.4% resulted from inferiorly located blebs.[38] It is encouraging, therefore, to report that there were no cases of bleb infection or endophthalmitis from this series, although nearly 50% of the blebs were described as cystic. Whilst it has been shown that lower IOPs are achieved with the use of adjunctive 5-FU in patients undergoing primary filtration surgery,[34,39] the presence of these large thin-walled cystic blebs undoubtedly represents a potential route of entry for bacterial pathogens and thus infection remains a risk.

A relatively high incidence of bleb-related sequelae (8 cases, 18%) was noted in this study. These comprised leaking bleb in 5 cases, hypotony maculopathy in 2 cases and giant bleb in 1 case. This has been the experience of other studies after filtering operations with post-operative 5-FU.[6–9,34,36,38,39] The increased incidence of bleb-related sequelae suggests a relative weakening of the bleb wall, most likely due to the toxic effect of 5-FU on the existing activated fibroblasts which has been reported experimentally[2–4] as well as in human eyes after trabeculectomy.[40]

In an era of peri-operative use of antimetabolites such as 5-FU and MMC, the possibility of late complications should always be considered. Due to its profound and permanent toxic effects on activated fibroblasts,[2,15] MMC produces blebs which tend to be thinner and more avascular than those seen with 5-FU. A recent paper describing trabeculectomy blebs after the use of MMC[41] showed that the conjunctiva had an irregular epithelium with a largely acellular and avascular substantia propria. Breaks in the basement membrane of the basal layer of the conjunctiva were also detected, which could allow slow transudation of aqueous through the bleb with the attendant risks of transient or chronic leaks, late infections or ruptures. In addition scleral necrosis, which has previously been recognised to occur following pterygium excision with adjunctive topical MMC,[42,43] has now recently been reported with the use of per-operative sponge MMC during trabeculectomy.[10]

Antimetabolites are certainly indicated in eyes with a high risk for post-operative scarring, and MMC in particular may have a role in cases of uveitis and neovascularisation, where a more prolonged inhibition of local fibroblast proliferation is required. This is supported by the results of a recent study in which the outcome of 5-FU filtering surgery for neovascular glaucoma (using post-operative injections) was poor, particularly in those under 50 years of age.[44] The results of this study confirm that the technique of applying 5-FU per-operatively to the sclera during trabeculectomy is a useful adjunctive treatment in low- to moderate-risk patients, at least in the short to medium term. It shares the same benefits of a single intraoperative exposure to MMC (i.e. removal of the need for post-operative injections and reduced incidence of corneal complications); however, due to its less prolonged and reversible effects on subconjunctival and scleral fibroblasts, it may be a safer treatment option. Nevertheless, 5-FU should be used with caution and its use in initial surgery in uncomplicated cases, as has been advocated by some,[34,39] under the current regimes and dosages, should be carefully considered. It is likely, however, that in future the doses of single applications of 5-FU could be varied in much the same way as those of MMC.[10–14] A concentration of 50 mg/ml was initially used because of the known efficacy of this dose in post-operative application, but it is likely that the release of 5-FU from the sponge is variable, as has been shown with MMC.[45] Indeed by altering concentration, sponge size or exposure time, unwanted side-effects could be minimised whilst preserving the IOP-lowering effect.

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Key words: Trabeculectomy, 5-Fluorouracil, Per-operative.

REFERENCES

1. Hitchings RA, Grierson I. Clinicopathological correlations in eyes with failed fistulising surgery. Trans Ophthalmol Soc UK 1983;103:84–8.
2. Khaw PT, Sherwood MB, MacKay SLD, Rossi MK, Schultz GS. Five minute treatments with fluorouracil, floxuridine and mitomycin have longterm effects on human Tenon's capsule fibroblasts. Arch Ophthalmol 1992;110:1150–4.
3. Khaw PT, Ward S, Porter A, Grierson I, Hitchings RA, Rice NSC. The longterm effects of 5-fluorouracil and sodium butyrate on human Tenon's fibroblasts. Invest Ophthalmol Vis Sci 1992;33:2043–52.
4. Yamamoto T, Varani J, Soong HK, Lichter PR. Effects of 5-fluorouracil and mitomycin C on cultured rabbit subconjunctival fibroblasts. Ophthalmology 1990;97:1204–10.
5. Salmon SE, Scatorelli AC. Cancer chemotherapy. In: Katzung BG, editor. Basic and clinical pharmacology. California: Lange Medical Publications, 1987:667–8.
6. The Fluorouracil Filtering Surgery Study Group. Five-year follow-up of the fluorouracil filtering surgery study. Am J Ophthalmol 1996;121:349–66.
7. Rockwood EJ, Parrish RK, Heuer DK, *et al.* Glaucoma filtering surgery with 5-fluorouracil. Ophthalmology 1987;94:1071.
8. Ruderman JM, Welch PB, Smith FM, Shoch DE. A randomised study of 5-fluorouracil and filtration surgery. Am J Ophthalmol 1987;104:218.
9. Nakano Y, Araie M, Sirato S. Effect of post-operative subconjunctival 5-fluorouracil injections on the surgical outcome of trabeculectomy in the Japanese. Graefes Arch Clin Exp Ophthalmol 1989;227:569.
10. Singh J, O'Brien C, Chawla HB. Success rate and complications of intraoperative 0.2 mg/ml mitomycin C in trabeculectomy surgery. Eye 1995;9:460–6.
11. Chen CW, Huang HT, Bair JS, Lee CC. Trabeculectomy with simultaneous application of mitomycin C in refractory glaucoma. J Ocul Pharmacol 1990;6:175–82.
12. Palmer SS. Mitomycin as adjunctive chemotherapy with trabeculectomy. Ophthalmology 1991;98:317–21.
13. Kitazawa Y, Suemori-Matsushita H, Yamamoto T, Kawase K. Low dose and high dose mitomycin trabeculectomy as an initial surgery in primary open angle glaucoma. Ophthalmology 1993;100:1624–8.
14. Skuta GL, Beeson CC, Higginbotham EJ, *et al.* Intraoperative mitomycin versus postoperative 5-fluorouracil in high risk glaucoma filtering surgery. Ophthalmology 1992;99:438–44.
15. Khaw PT, Doyle JW, Sherwood MB, Grierson I, Schultz GS, McGorray S. Prolonged localised tissue effects from 5 minute exposures to 5-fluorouracil and mitomycin C. Arch Ophthalmol 1993;111:263–7.
16. Jampel HD, Pasquale LR, Dibernardo C. Hypotony maculopathy following trabeculectomy with mitomycin C. Arch Ophthalmol 1992;110:1049–50.
17. Higginbotham EJ, Stevens RK, Musch DC, Karp KO, Lichter PR, Bergstrom TJ, Skuta GL. Bleb-related endophthalmitis after trabeculectomy with mitomycin C. Ophthalmology 1996;103:650–6.
18. The Fluorouracil Filtering Surgery Study Group. Fluorouracil filtering surgery study: one year follow-up. Am J Ophthalmol 1989;108:625–35.
19. Lanigan L, Sturmer J, Baez KA, Hitchings RA, Khaw PT. Single intraoperative applications of 5-fluorouracil during filtration surgery: early results. Br J Ophthalmol 1994;78:33–7.

20. Egbert PR, Williams AS. Singh K, Dadzie P, Egbert TB. A prospective trial of intraoperative fluorouracil during trabeculectomy in a black population. Am J Ophthalmol 1993;116:612–6.
21. Dietze PJ, Feldman RM, Gross RL. Intraoperative application of 5-fluorouracil during trabeculectomy. Ophthalmic Surg 1992;23:662–5.
22. Mora JS, Nguyen N, Iwach AG, *et al.* Trabeculectomy with intraoperative sponge 5-fluorouracil. Ophthalmology 1996;103:963–70.
23. Singh J, Bell RWD, Adams A. O'Brien C. Enhancement of post-trabeculectomy bleb formation by laser suture lysis. Br J Ophthalmol 1996;80:624–7.
24. Heuer DK, Parrish RK II, Gressel MG, Anderson DR, Hodapp E, Palmberg PF. Trabeculectomy in aphakic eyes. Ophthalmology 1984;91:1045–51.
25. Stewart RH, Kimbrough RL, Bach H, Allbright M. Trabeculectomy and modifications of trabeculectomy. Ophthalmic Surg 1979;10:76–80.
26. Heuer DK, Parrish RK II, Gressel MG, *et al.* 5-Fluorouracil and glaucoma filtering surgery. III. Intermediate follow-up of a pilot study. Ophthalmology 1986;93:1537–46.
27. Lavin MJ, Wormald RPL, Migdal CS, Hitchings RA. The influence of prior therapy on the success of trabeculectomy. Arch Ophthalmol 1990;108:1543–8.
28. Broadway DC, Grierson I, O'Brien C, Hitchings RA. Adverse effects of topical antiglaucoma medication. I. The conjunctival cell profile. Arch Ophthalmol 1994;112:1437–45.
29. Broadway DC, Grierson I, O'Brien C, Hitchings RA. Adverse effects of topical antiglaucoma medication. II. The outcome of filtration surgery. Arch Ophthalmol 1994;112:1446–54.
30. Miller RD, Barber JC. Trabeculectomy in black patients. Ophthalmic Surg 1981;12:46–50.
31. Sturmer J, Broadway DC, Hitchings RA. Young patient trabeculectomy: assessment of risk factors for failure. Ophthalmology 1993;100:928–39.
32. Weinreb RN. Adjusting the dose of 5-fluorouracil after filtration surgery to minimise side effects. Ophthalmology 1987;94:564–70.
33. Freyer EB, Chaturvedi N, Zurakowski D. Effect of mitomycin C and fluorouracil-supplemented trabeculectomies on the anterior segment. Arch Ophthalmol 1995;113:578–80.
34. Whiteside-Michael J, Liebmann JM, Ritch R. Initial 5-fluorouracil trabeculectomy in young patients. Ophthalmology 1992;99:7–13.
35. Prata JA, Seah SKL, Minckler DS, *et al.* Postoperative complications and short-term outcome of 5-fluorouracil or mitomycin C trabeculectomy. J Glaucoma 1995; 4:25–31.
36. Ticho U, Ophir A. Late complications after glaucoma filtering surgery with adjunctive 5-fluorouracil. Am J Ophthalmol 1993;115:506–10.
37. Stamper RL, McMenemy MG, Lieberman MF. Hypotonous maculopathy after trabeculectomy with subconjunctival 5-fluorouracil. Am J Ophthalmol 1992; 114:544–53.
38. Wolner B, Liebmann JM, Sassani JW, Ritch R, Speaker M, Marmor M. Late bleb-related endophthalmitis after trabeculectomy with adjunctive 5-fluorouracil. Ophthalmology 1991;98:1053–60.
39. Liebmann JM, Ritch R, Marmor M, Nunez J, Warner B. Initial 5-fluorouracil trabeculectomy in uncomplicated glaucoma. Ophthalmology 1991;98:1036–41.
40. Ophir A, Ticho U. Toxic effects of 5-fluorouracil on fibroblasts following trabeculectomy. Ophthalmic Res 1992;24:298.
41. Mietz H, Brunner R, Addicks K, Krieglstein GK. Histopathology of an avascular filtering bleb after trabeculectomy with mitomycin C. J Glaucoma 1993; 2:266–70.
42. Rubinfield RS, Pfister RR, Stein RM, *et al.* Serious complications of topical mitomycin C after pterygium surgery. Ophthalmology 1992;99:1647–54.
43. Fujitani A, Hayasaka S, Shibuya Y, Noda S. Corneoscleral ulceration and corneal perforation after pterygium excision and topical mitomycin C. therapy. Ophthalmologica 1993;207:162–4.
44. Tsai JC, Feuer WJ, Parrish RK II, Grajewski AL. 5-Fluorouracil filtering surgery and neovascular glaucoma: longterm follow-up of the original pilot study. Ophthalmology 1995;102:887–92.
45. Yamamoto T, Kitazawa Y. Residual mitomycin C dosage in surgical sponges removed at the time of trabeculectomy. Am J Ophthalmol 1994;117:672–3.