CLINICAL STUDY

Is the single use of intraoperative 5-fluorouracil in filtering surgery for high-risk cases enough?

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Abstract

Purpose **To study the efficacy of the adjunctive use of a single intraoperative application of 5-fluorouracil (5FU) in eyes with poor prognoses for a successful outcome with a trabeculectomy.**

Method **Twenty-four patients (25 eyes) with a mean age of 63.7 ± 14.7 years (range 27–86 years) and a history of one or more risk factors (age <50 years, more than 3 years on topical medication, a previous failed filter, previous cataract surgery, uveitis, neovascular glaucoma) underwent trabeculectomy with the intraoperative application of 5FU on a sponge (25 mg/ml) for 5 min. The average follow-up was 10.1 ± 5.5 months.**

Results **The mean pre-operative intraocular pressure (IOP) was 24.7 ± 6.2 mmHg and the mean post-operative IOP was 13.9 ± 3.5 mmHg. Success, defined as an IOP within desired target levels for a particular eye, in the presence of a functioning filter, without supplementary medical therapy, was achieved in 56.5% of cases.**

Conclusions **Our results of successful filters in this group of patients with moderate- to high-risk characteristics approach similar figures quoted for trabeculectomies without the adjunctive use of intraoperative 5FU in eyes with poor prognoses with a similar length of follow-up. Though the numbers are small there is a trend that indicates that the intraoperative application of a single dose of 5 FU alone may not be sufficient in eyes with moderate- to high-risk characteristics of failure of a trabeculectomy.**

Key words 5-Fluorouracil, Trabeculectomy

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A major cause of failure of filtering surgery is the proliferation of fibroblasts post-operatively.[1–5] The administration of 5-fluorouracil (5FU), an antimetabolite that inhibits fibroblast proliferation by both its inhibition of thymidilate synthetase and its incorporation into the RNA molecule, has improved the success rate of filtering surgery.[6,7]

Initially the route of administration was by twice-daily injections during the first week after filtering surgery and once-daily injections during the second week;[8] the frequency of administration was subsequently reduced with no apparent reduction in the success rate.[9] This method of administration is painful, involves a number of post-operative visits, is associated with significant corneal epithelial toxicity and has an increased incidence of post-operative wound leak.[8,10] A single intraoperative application of 5FU at the site of filtering surgery largely avoids the above problems associated with post-operative injections and is presently the current practice. The initial results reported are encouraging.[11]

We present our initial experience with the single intraoperative application of 5FU in patients with low/moderate- to high-risk characteristics for filtering surgery failure.

Materials and methods

Twenty-four consecutive patients (25 eyes) were recruited for this study between 1993 and 1995 (both the eyes of patient 8 were included). Inclusion criteria were uncontrolled glaucoma on maximally tolerated medical therapy and low/moderate- to high-risk factors for failure of filtering surgery. Exclusion criteria were previous filtering surgery with the use of an antimetabolite or post-operative 5FU injections.

The risk factors are outlined in Table 1. A stratification of risk factors into high-risk (major) and low-risk (minor) was chosen as it is patients in the high-risk group who have a poor prognosis for successful filtering surgery.[12] All the pseudophakic patients included had conjunctival incisional surgery. A previous similar classification of risk factors has been used by Lanigan *et al.*[11] The demographic characteristics of the patients are listed in Table 2, which includes both eyes of patient 8.

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Table 1. *Risk factors for filtering surgery*

Main risk factors	
Uveitis	1
Neovascular glaucoma	1
Previous trabeculectomy	14
Pseudophakia	9
Minor risk factors	
Age less than 50 years	4
Afro-Caribbean/Asian origin	2
More than 3 years on topical medications	17

Low risk: One or two minor risk factors.
Moderate risk: Three minor risk factors.
High risk: Presence of any of the major factors.

A trabeculectomy was performed (by P. W. and J. M.) as described elsewhere,[13] with a limbal-based conjunctival flap and a scleral flap 4 mm × 4 mm in size. The 5FU (David Bull Laboratories, Warwick, UK) was applied on sponges to both sides of the dissected scleral flap (sandwich technique), before the anterior chamber was entered. The sponges (microsponge, Alcon), cut freehand, measured about 5 mm × 2 mm × 1 mm when soaked with the 5FU solution. The concentration used was 25 mg/ml. The top sponge was resoaked every minute and reapplied for a total time of 5 min, taking care not to touch the free cut edge of the conjunctiva. The area was washed with 10 ml of balanced salt solution (Alcon) then dried, and the trabeculectomy completed with a 2 mm × 2 mm block of trabecular tissue excised freehand. A peripheral iridectomy was performed and the scleral flap closed with an average of two 10-0 nylon interrupted sutures depending on the number necessary to keep the anterior chamber formed. The conjunctival incision was closed with an 8-0 continuous Vicryl suture. A subconjunctival injection of betamethasone and

Table 2. *Demographic characteristics of the patients and summary of the results*

Patient no.	Age/Sex	Race	Diagnosis	Pre-op. IOP (mmHg)	Post-op. IOP (mmHg)	Medication	Post-op. medication	Risk factors
1	76/F	C	CACG	21	16	2	2	Failed trabeculectomy, pseudophakia, > 3 years on topical medication
2	56/M	C	POAG	23	19	4	4	Two failed trabeculectomies, > 3 years on topical medication
3	69/M	C	SOAG	48	18	2	1	Pseudophakia, vitrectomy
4	86/F	C	POAG	20	15	2	2	Pseudophakia, failed trabeculectomy, > 3 years on topical medication
5	82/F	C	POAG	24	18	3	1	Two failed holmium laser sclerostomies, > 3 years on topical medication
6	79/M	C	POAG	22	12	2	0	Failed holmium laser sclerostomy, > 3 years on topical medication
7	86/F	C	POAG	22	17	2	1	Pseudophakia, > 3 years on topical medication
8	67/M	C	POAG	26	15	3	0	Failed trabeculectomy, > 3 years on topical medication
8	67/M	C	POAG	21	10	3	0	Failed trabeculectomy, > 3 years on topical medication
9	59/M	C	CACG	28	17	3	3	Failed trabeculectomy
10	61/M	C	POAG	24	9	2	0	Failed trabeculectomy, > 3 years on topical medication
11	71/M	C	POAG	19	15	2	0	Pseudophakia, > 3 years on topical medication
12	39/M	C	POAG	27	8	3	0	Age < 50 years, > 3 years on topical medication
13	76/M	C	SOAG	26	14	2	3	Pseudophakia, vitrectomy
14	71/M	C	NVG	–	–	2	–	Neovascular glaucoma
15	65/F	A	POAG	28	8	2	0	Asian
16	49/F	C	POAG	24	8	2	0	Age < 50 years
17	55/M	C	POAG	21	12	3	0	Failed trabeculectomy, > 3 years on topical medication
18	52/M	C	POAG	31	11	2	2	Pseudophakia, failed trabeculectomy, penetrating corneal graft, > 3 years on topical medication
19	50/M	C	SOAG	38	–	2	2	Pseudophakia, uveitis
20	74/F	C	POAG	32	18	2	0	Failed holmium sclerostomy, failed trabeculectomy, > 3 years on topical medication
21	74/F	A	POAG	20	12	2	0	Pseudophakia, > 3 years on topical medication
22	61/M	C	POAG	21	15	1	0	Failed trabeculectomy, Asian
23	41/M	C	POAG	20	18	2	0	Failed trabeculectomy, age < 50 years, > 3 years on topical medication
24	27/M	C	POAG	22	16	2	2	Age < 50 years

C, Caucasian; A, Asian; POAG, primary open angle glaucoma; CACG, chronic angle closure glaucoma; SOAG, secondary open angle glaucoma; NVG, neovascular glaucoma; IOP, intraocular pressure.

cefuroxime was given at the end of the procedure and a drop of atropine 1% instilled.

Follow-up visits were on day 1, week 1, week 2, week 4, 2 months and 6 months post-operatively. Additional visits were dictated by the condition of the patient.

The post-operative regimen of drops included a steroid antibiotic combination (dexamethasone, neomycin and polymixin B sulphate) for 2 weeks followed by a tapering dose of dexamethasone for 12 weeks post-operatively.

Success was defined as complete or qualified. Complete success was an intraocular pressure that was considered safe for that particular optic nerve (target pressure), without supplementary medical therapy, in the presence of a functioning filter. Qualified success was as above but with the help of supplementary medical therapy.

Results

Of the 24 patients, one was lost to follow-up (patient 14) and another was excluded as he received supplementary post-operative 5FU injections (patient 19). Hence 23 eyes that received a single intraoperative dose of 5FU were included in the analysis of the data. The mean age of the patients was 63.7 ± 14.7 years (range 27–86 years). The mean pre-operative IOP was 24.7 ± 6.2 mmHg and the mean post-operative IOP was 13.9 ± 3.5 mmHg. The number of pre-operative medications received was 2.3 ± 0.61 and the mean supplementary medical therapy received was 0.96 ± 1.2. Thirteen eyes (13/23; 56.5%) were complete successes; a further eye was a qualified success. The mean duration of follow-up was 10.1 ± 5.5 months (range 3–24 months). The patients maintained the level of pre-operative visual acuity and visual fields throughout follow-up.

The post-operative complications included a shallow anterior chamber (AC) in one patient, a flat AC without keratolenticular contact, wound leak in two patients, early hypotony in two patients, and <2 mm hyphaemas in two patients. All these complications resolved with conservative management (Table 3).

Both the patients in the low-risk category were successes; one patient (1 of 2 eyes) in the moderate-risk group failed. Nine eyes (9 of 19 eyes) in the high-risk group were successful (47.3%). The Kaplan-Meier survival estimates demonstrate the probability of successful IOP control after intraoperative use of 5FU during a trabeculectomy (Fig. 1).

Table 3. *Post-operative complications*

Shallow anterior chamber	1
Flat anterior chamber (no keratolenticular contact)	1
Wound leak	2
Early hypotony	2
Hyphaema	2

Discussion

The introduction of post-operative subconjunctival injections of 5FU has improved the success rate of filtering surgery in high-risk patients.[12,14–16] The optimal route of administration, however, seems to be a single intraoperative application of 5FU on a sponge. It offers several advantages over the injections, in that it avoids multiple post-operative visits, there is no pain associated with its application, the corneal epithelium is unaffected and wound leaks are uncommon. In addition the drug is delivered at the site where it is required to offset the fibrosis associated with failure. The drawback of a single intraoperative application of 5FU on a sponge is that the dose cannot be measured or titrated.[11]

The initial results reported by Lanigan *et al.*[11] were encouraging, with a success rate of 91% (100% if the results of only the low- to moderate-risk category were considered) with a limited follow-up (of 3–9 months). In the first year of follow-up of the Fluorouracil Filtering Surgery Study (FFSS) there was a 73% success rate in patients with moderate- to high-risk characteristics, compared with a 50% success rate for the control group.[14]

The success rate in the group of patients presented here was 56.5% (60.8% qualified successes were included) over a follow-up ranging from 3 to 24 months (mean 10.1 ± 5.5 months). If our two low-risk category patients were excluded the success rate was 47.3% (9/19). This is similar to the controls of the FFSS group with comparable lengths of follow-up. This trend from our study seems to suggest that the single application of intraoperative 5FU offers no advantage in the moderate-to high-risk category. The results are at odds with previous studies (Table 4), which may be explained by the differing risk categories, different lengths of follow-up, and differing criteria for success.

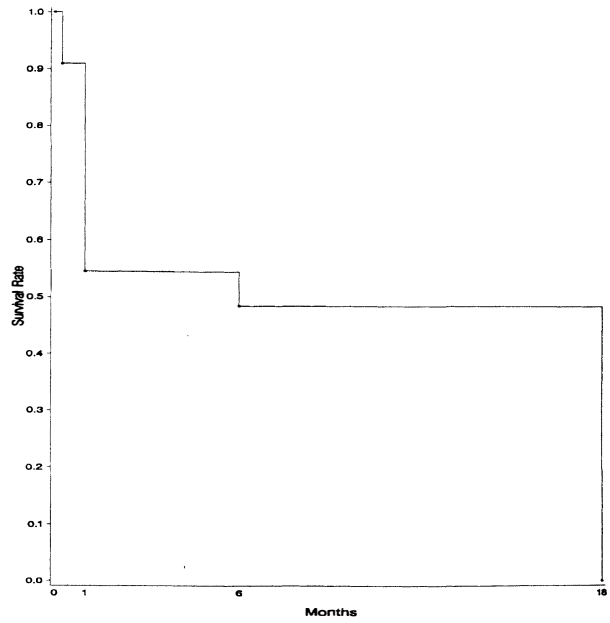

Fig. 1. *Estimated probability of survival of successful IOP control (Kaplan-Meier survival estimates) in moderate- to high-risk cases.*

Table 4. *Results of previous studies*

Authors	Year	Route of administration	No. of patients (risk)	Success rate		Follow-up
				5FU	Controls	
Smith *et al.*[24]	1992	Sponge (50 mg/ml) + injections	14 (7 low, 7 high)	93%	–	6.4 months
Lanigan *et al.*[11]	1994	Sponge (25 mgl/ml)	33 (low/high)	91%	–	5.7 months
Mora *et al.*[17]	1996	Sponge (50 mg/ml) + injections	119 (low/high)	86.4%	–	16.0 months
Singh *et al.*[18]	1997	Sponge (50 mg/ml)	37 (low)	73%	–	3 months
Bell *et al.*[19]	1997	Sponge (25 mg/ml) + injections	45 (low/moderate/high)	80%	–	24 months
Ruderman *et al.*[25]	1987	Injections (45 mg)	14 (high)	85%	25%	12 months
Ophir *et al.*[21]	1992	Injection (20–30 mg)	41 (low)	96%	76%	17.5 months
FFSS[14]	1989	Injections (105 mg)	105 (high)	73%	50%	1 year
FFSS[15]	1993	Injections (105 mg)	100 (high)	51%	26%	3 years
FFSS[16]	1996	Injections (105 mg)	105 (high)	49%	26%	5 years

Mora *et al.*[17] reported a success rate of 86.4%. The shortest length of follow-up was 2 months, the concentration of 5FU was 50 mg/ml and the majority of eyes received an average of 5.3 supplementary 5FU injections post-operatively, which may explain the improved success rate.

In a black population from Ghana, Singh *et al.*[18] reported a success rate of 73% (IOP <21 mmHg). This differs from our population group, in addition to the fact that the concentration of 5FU was 50 mg/ml and the technique of application differed slightly.

Bell *et al.*[19] reported a success rate of 80% on or off supplementary medical therapy, with no difference between the high- or low-risk groups, with a mean follow-up of 24 months. If only the complete successes were considered, the percentage dropped to 48.8%. Amongst the complete successes there were 8 of 11 patients (73% success rate) in the low/moderate-risk groups (our classification) and 14 of 34 (41.1% success rate) in the high-risk category. The latter figures do correlate with the figures in our high-risk category. This study differs from ours in that the authors used post-operative 5FU injections if there were signs of bleb failure, and the technique of application was slightly different in that the 5FU was applied before the scleral dissection.

The 5 year follow-up of the FFSS recently reported a further drop-off in the success rate, and at the end of the study period 49% of eyes maintained successful filters compared with 26% in the control group.[16] It is possible that the percentage of successful cases in our series will fall with a longer follow-up.

Though not comparable in terms of mode of 5FU application, when the results for the first year of the FFSS are compared with those of our study, it would seem reasonable to suggest that the dose delivered by a single intraoperative application of 5FU on a sponge is insufficient to improve the success rate of filtering surgery in patients who present with high-risk characteristics.

It is not known whether a higher concentration of the drug (50 mg/ml; not commerically available in the UK) would offer any advantage over the 25 mg/ml concentration. Khaw *et al.*[20] have shown that a very short exposure (5 min) of human Tenon's capsule fibroblasts to 5FU restricted the increase in the number of cells for long periods and hence a single application at the time of surgery should negate the need for repeated post-operative injections. It could be postulated either that high-risk patients have an increased resident population of fibroblasts whose outgrowth is not sufficiently suppressed by the single intraoperative application of 5FU or that the duration of suppression in this group is not adequate.

Ophir *et al.*[21] reported a successful result in 96% of their patients with no risk factors who received adjunctive 5FU injections, with an average follow-up period of 17.5 months; the success rate in controls was 76%. These results are similar to figures presented for the use of intraoperative 5FU application in low- to moderate-risk groups.[11] Though these groups are not strictly comparable (Table 4), the conclusion one could draw from them and our study is that the single use of 5FU intraoperatively may prolong the survival of filtering procedures in patients with either no risk factors or low to moderate risk factors.

The use of intraoperative 5FU at best achieves a reversible delay of fibroblast proliferation; animal studies suggest that this may be as short as 1 week.[22] Hence the patients with high-risk characteristics may require a 'fibrocidal' antimetabolite such as mitomycin C[23] or prolonged administration of 5FU injections in addition to the dose applied intraoperatively on a sponge. Smith *et al.*[24] reported a success rate of 93% in a mixed group of patients who received adjunctive 5FU on a sponge together with post-operative injections; however, this regime negates some of the advantages offered by a single intraoperative application, except that the number of post-operative injections may be reduced.

Conclusion

This small group of patients with a reasonable follow-up period demonstrate a trend that a single intraoperative application of 5FU on a sponge is insufficient alone to enhance the success of filtering surgery in patients with high-risk characteristics.

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