CLINICAL STUDY

Delayed post-operative use of 5-fluorouracil as an adjunct in medically uncontrolled open angle glaucoma

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Abstract

Purpose **The current study was performed to evaluate the efficacy and safety of late post-operative use of subconjunctival 5-fluorouracil (5-FU) with ocular massage (OM) after trabeculectomy with or without intraoperative mitomycin C (MMC) in patients with medically uncontrolled primary open angle glaucoma (POAG).**

Methods **Initial trabeculectomy was performed in 60 eyes of 60 consecutive patients with medically uncontrolled POAG. Thirty eyes (group 1) were randomly assigned to intraoperative MMC (0.2 mg/ml for 3 min) and 30 (group 2) were randomised to standard trabeculectomy. During the first 3 months post-operatively OM and subconjunctival injections of 5-FU (5 mg in 0.5 ml of balanced salt solution) were performed in both groups every time the clinical evaluation suggested imminent bleb failure. Suture lysis was not performed in any patient.**

Results **Follow-up ranged from 14 to 53 months (mean 30.17, SD 9.23) in trabeculectomy + MMC treated eyes and from 6 to 54 months (mean 27.37, SD 10.83) in trabeculectomy treated eyes. During the first 3 months of follow-up OM and subconjunctival injections of 5-FU were performed in 14 cases in group 1 and in 18 cases in group 2 (p = NS). A positive response to OM was obtained in 14 of 14 eyes and in 14 of 18 eyes in group 1 and in group 2, respectively (p = 0.042). The difference in post-operative mean IOP between the two groups was statistically significant at each time interval studied ($p < 0.001$). Success (complete or qualified) was achieved in 50 of 60 eyes (83.33%): 28 (93.3%) in the trabeculectomy + MMC treated group and 22 (73.3%) in the trabeculectomy treated group (p = 0.039). Among the complications seen, the incidence of bleb fibrosis was higher in group 2 (p = 0.0026). By means of post-operative treatment four non-randomised subgroups were identified: intraoperative MMC + post-operative 5-FU, intraoperative MMC + no post-operative 5-FU, no intraoperative MMC + post-operative 5-FU, no intraoperative MMC + no post-operative 5-FU. The eyes treated with intraoperative MMC and post-operative 5-FU had a better long-term (48 months) cumulative probability of success (100%); treatment with intraoperative MMC or post-operative 5-FU alone was followed by a success rate of 87.1% and 72.2%, respectively. The cumulative probability of success after only trabeculectomy was 56% ($p < 0.05$). One case of hypotony maculopathy was found in the subgroup treated only with intraoperative MMC.**

Conclusions **This study confirms the effectiveness and relative safety of delayed post-operative 5-FU treatment in patients with clinical evidence of bleb failure. Only when OM had caused a lowering of IOP were late subconjunctival injections of 5-FU followed by good control of IOP. The use of intraoperative MMC may ensure a greater IOP decrease after OM.**

Key words Antimetabolite, Ocular massage, Primary open angle glaucoma, Trabeculectomy

Subconjunctival injections of 5-fluorouracil (5-FU) improve intraocular pressure (IOP) control after glaucoma filtration surgery.[1–6] Most studies have evaluated the effect of 5-FU on high-risk eyes, but recent studies demonstrate that 5-FU injections also improve IOP control in eyes undergoing initial filtration surgery.[7–11]

The dosage regimen recommended by the Fluorouracil Filtering Surgery Study Group (FFSSG)[1-6] has been associated with conjunctival wound leaks and corneal epithelial defects.[6,12–14] It has recently been suggested that injections be started only when clinical evidence suggests that bleb failure is likely.[3,15] Hefetz *et al.*[16] suggest that application of 5-FU at a relatively late post-operative point can still effectively control IOP.

In the current study we evaluated the efficacy and safety of late post-operative use of subconjunctival 5-FU with ocular massage (OM) after trabeculectomy with or without

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intraoperative mitomycin C (MMC) in patients with advanced primary open-angle glaucoma.

Materials and methods

From January 1992 to December 1994, initial trabeculectomy was performed in 60 eyes of 60 consecutive white Caucasian patients with medically uncontrolled primary open-angle glaucoma. Informed consent to participate in this study was obtained from all subjects after they had been given a detailed description of the procedures to be used and the aims of the study. Local ethics committee permission for the study was obtained.

Thirty eyes were randomised to receive intraoperative MMC (group 1) and 30 were randomised to simple trabeculectomy. Eyes were matched according to age, gender, pre-operative IOP and previous management (Table 1). In all patients the operations were performed or directly supervised by the same surgeon (P.E.G.). Limbal-based conjunctival flaps were created in all eyes.

In group 1 we added intraoperative administration of MMC (Kyowa Hakko Kogyo, Tokyo) to the filtration surgery. A section of Weck-cel sponge (5 × 5 mm) was placed into a sterile container containing 2 ml of a 0.2 mg/ml MMC solution. By measuring the amount of solution remaining in the container after withdrawing the sponge it could be stated that after soaking there were 0.2 ml of solution in the sponge. The sponge was placed between the conjunctiva/Tenon's capsule and sclera before the rectangular partial-thickness scleral flap was created. The edge of the conjunctiva was gently handled with smooth forceps and the conjunctiva draped over the sponge. After 3 min the sponge was removed and the treated tissues rinsed thoroughly with 20 ml of balanced salt solution.

After creating a 3.0 × 4.0 mm rectangular scleral flap, one third to one half scleral thickness, a paracentesis opening was made, a 1.0 × 2.0 mm deep scleral block beneath the scleral flap was removed and a peripheral iridectomy was performed. The scleral flap was closed with four interrupted 10-0 nylon sutures. The conjunctiva and Tenon's layer were closed simultaneously with single running 8-0 virgin silk sutures. Finally, balanced salt solution was injected through the paracentesis opening to elevate the conjunctival bleb, test flow through the trabeculectomy, and check for wound leaks. After surgery, 1.5 mg of betamethasone acetate was injected subconjunctivally in the inferior fornix.

Table 1. *Patient characteristics and previous management in groups 1 and 2*

	Trabeculectomy with adjunctive mitomycin C (group 1)	Trabeculectomy (group 2)
Patients characteristics		
Age (years)		
Mean	65.6 ± 8.1	64.9 ± 7.9
Range	51–83	52–79
Gender		
Women	8 (26.7%)	7 (23.3%)
Men	22 (73.3%)	23 (76.7%)
Pre-operative IOP (mmHg)		
Mean	29.5 ± 4.6	29.1 ± 5.2
Range	23–51	24–48
Previous management		
No. of glaucoma medications		
Mean	3 ± 0.8	3 ± 0.7
Range	2–4	2–4
Previous argon laser trabeculoplasty (no. of eyes)	18 (60%)	19 (63.3%)

All patients received a similar topical medical regimen in the post-operative period, including 1% solution of topical atropine sulphate twice daily, 0.2% solution of dexamethasone three times daily and 0.3% drops of tobramicin four times daily.

Patients were examined daily in the first post-operative week, weekly in the first month, monthly in the first 6 months and then every 3 months. All patients were examined by a clinician masked to the treatment. At each post-operative visit patients were fully examined at the slit lamp, and visual acuity, IOP and bleb appearance were determined.

At control examinations we evaluated the incidence of side effects and complications such as corneal epithelial defects, conjunctival bleb leaks, anterior chamber inflammatory reaction, hypotony, choroidal effusions and bleb fibrosis.

In the post-operative follow-up OM was performed using the technique suggested by Traverso *et al.*[17] every time the tonometric evaluation suggested imminent bleb failure. One of the following criteria for impending bleb failure was used: IOP ⩾ 25 mmHg, or IOP ⩾ 21 mmHg with either progressive increase in IOP value (at least 3 mmHg) from the previous visit or the clinical appearance of imminent bleb failure (progressive increase in vascularisation of the conjunctiva overlying the surgical site and/or flattening of the bleb). Additional subconjunctival injections of 5-FU (fluorouracil iketon, ABIC, Israel; 5 mg in 0.5 ml of balanced salt solution) were performed in eyes with impending bleb failure. The injections were given 180° from the surgical site, 10 mm from the limbus via a 30 gauge needle. Patients who received injections were seen sooner than the prescribed frequency. They came back every 3 days until receiving subconjunctival 5-FU. Additional 5-FU injections were only given within the first 3 post-operative months and were stopped when patients no longer met the criteria for impending bleb failure. No form of suture lysis was used.

Pre-operative baseline information was obtained for each patient, including age, sex, previous management, visual acuity, IOP and ocular medications. Post-operative data were collected at each post-operative visit.

Difference in post-operative IOP between the MMC group and trabeculectomy group was studied at 6 months, 1 year and at the last visit. Complete success was defined as an IOP of less than 22 mmHg and greater than 4 mmHg without glaucoma medication. The operation was considered a qualified success when the IOP was less than 22 mmHg with glaucoma medication (including oral carbonic anhydrase inhibitor), a qualified

failure when the IOP was greater than 21 mmHg with glaucoma medication, and a complete failure when an eye required an additional glaucoma filtering operation or developed devastating complications. In case of failure (qualified or complete) follow-up was stopped.

For statistical analysis we used a statistical software package (SPSS, release 6.0, 444 N. Michigan Ave, Chicago, IL). Comparisons between the two groups were performed by using comparison of means in paired samples, and a Fisher exact test and chi-squared analysis for 2 × 2 tables. Success rates were calculated employing the chi-squared test and 'life-table analysis' to calculate the survival curve by the Kaplan–Meier method; the difference between survival curves was tested by the log-rank test. The success rates calculated by the Kaplan–Meier method differ from those of cross-sectional analysis because they represent the cumulative probability of success based only on patients who have not yet failed or dropped out and they exclude a patient from further analysis once that patient has failed.[18] The probabilities estimated from each of the time intervals are used to estimate the overall probability of the event occurring at different time points.[19] Using the algorithm of Lee and Desu[20] it was possible to calculate whether the survival distributions were the same for the four subgroups: trabeculectomy with intraoperative MMC + post-operative 5-FU, trabeculectomy with intraoperative MMC without post-operative 5-FU, trabeculectomy without intraoperative MMC + post-operative 5-FU, trabeculectomy without MMC without 5-FU. Intercurve analysis was performed by using the log-rank test. A p value less than or equal to 0.05 was considered statistically significant.

Results

Follow-up ranged from 14 to 53 months (mean 30.17, SD 9.23) in trabeculectomy + MMC treated eyes (group 1) and from 6 to 54 months (mean 27.37, SD 10.83) in trabeculectomy treated eyes (group 2).

During the first 3 months of follow-up OM was performed in 14 cases in group 1 and in 18 cases in group 2 (p = NS). A positive response to OM was obtained in 14 of 14 eyes and in 14 of 18 eyes in group 1 and in group 2, respectively ($p = 0.042$). The mean pre-operative IOP values in the two groups on maximum treatment were similar (29.5 ± 4.6 mmHg and 29.1 ± 5.2 mmHg) (Table 1). The difference in post-operative mean IOP between the two groups was statistically significant at 6 months, 1 year and at the last visit (Table 2). Success (complete or qualified) was achieved in 50 of 60 eyes (83.33%): 28 (93.3%) in the trabeculectomy + MMC treated group and 22 (73.3%) in the trabeculectomy treated group ($p = 0.039$) (Table 3).

Post-operative 5-FU injections were performed in both groups within the first 3 months, as shown in Table 4. The mean number of 5-FU injections differed significantly between the two groups (4.6 ± 0.7 and 5.6 ± 0.5 injections in groups 1 and 2, respectively; $p < 0.001$). Using a Kaplan–Meier survival curve, after 48 months of follow-up the cumulative probability of success is 92.2% in group 1 and 61.9% in group 2 ($p < 0.05$) (Fig. 1).

The eyes treated with intraoperative mitomycin C and post-operative 5-FU had a better long-term (48 months) cumulative probability of success (100%); treatment with intraoperative MMC or post-operative 5-FU alone is followed by a success rate of 87.1% and 72.2%, respectively. The cumulative probability of success after trabeculectomy only was 56% ($p < 0.05$; Fig. 2).

Pre-operatively there was no statistically significant difference in the number of medications used in the two groups.

Early and late post-operative complications are listed in Table 5.

Table 2. *Mean intraocular pressure post-operatively*

Post-operative IOP (mmHg)	Trabeculectomy with adjunctive mitomycin C (group 1)	Trabeculectomy (group 2)	p
6 months			0.004
Mean	10.5 ± 6.9	16.3 ± 8.1	
Range	3–26	6–35	
12 months			<0.001
Mean	11.8 ± 5.5	18.1 ± 7.5	
Range	4–20	7–38	
Last visit			<0.001
Mean	13.3 ± 4.9	20.0 ± 7.3	
Range	4–21	9–41	

Table 3. *Follow-up and surgical outcome*

	Trabeculectomy with adjunctive mitomycin C (group 1)	Trabeculectomy (group 2)
Follow-up (months)		
Mean	30.17 ± 9.23	27.37 ± 10.83
Range	14–53	6–54
Surgical outcome		
Success	28 (93.3%)	22 (73.3%)[a]
Complete	24 (80%)	12 (40%)
Qualified	4 (13.3%)	10 (33.3%)
Failure	2 (6.7%)	8 (26.7%)
Qualified	2 (6.7%)	6 (20%)
Complete	–	2 (6.7%)
Post-operative medication per patient		
Mean ± SEM	0.3 ± 0.07	1.2 ± 0.24[b]
Range	0–1	0–4
Ocular massage (OM)	14 (46.7%)	18 (60%)
Positive response to OM	14/14 (100%)	14/18 (77.7%)[c]
No. of eyes receiving 5-FU injections post-operatively	14 (46.7%)	18 (60%)
Visual outcome		
Same or better	28 (93.3%)	25 (83.3%)
Worse[d]	2 (6.7%)	5 (16.7%)

[a] $p = 0.039$, Fisher exact test; [b] $p < 0.001$, unpaired t-test;
[c] $p = 0.042$, χ^2 analysis.
[d] Reduction of two or more lines in Snellen visual acuity.

Table 4. *Post-operative 5-FU treatment in the two groups*

	Trabeculectomy with adjunctive MMC (group 1)	Trabeculectomy (group 2)
First month		
No. of patients receiving 5-FU	5	9
No. of injections	15	27
Second month		
No. of patients receiving 5-FU	12	17
(new patients)	(7)	(8)
No. of injections	40	63
Third month		
No. of patients receiving 5-FU	6	7
(new patients)	(2)	(1)
No. of injections	10	11
Total no. of patients receiving 5-FU	14	18
Total no. of injections	65	101
Mean no. of injections[a]	4.6 ± 0.7	5.6 ± 0.5[b]

[a]Referred just to the patients who received post-operative 5-FU injections.
[b]$p < 0.001$, unpaired *t*-test.

Discussion

Most studies of 5-FU treatment in glaucoma filtering surgery show that its antimetabolic activity is associated with complications such as corneal epithelial defects and conjunctival wound leaks.[1–14] Hefetz *et al.*[16] suggested that application of 5-FU at a relatively late post-operative time, based on clinical evidence of impending bleb failure, can still increase the operative success rate, minimising the use of this potentially hazardous medication.

In our study post-operative 5-FU injections were performed within the first 3 months only when clinical evidence suggested that bleb failure was likely. Criteria for impending bleb failure were similar to those used by other authors.[16,21]

Cotton-tip OM was performed in eyes with impending bleb failure. OM is a therapeutic technique of applying direct, focal pressure to an eye after glaucoma filtering surgery. Purposes include reducing IOP, identifying a failing bleb or enhancing outflow. There

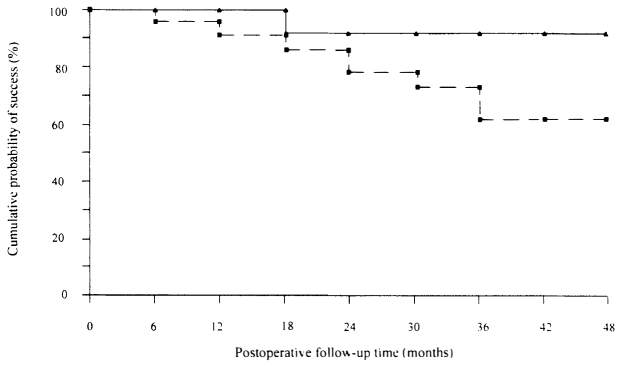

Fig. 1. *Survival curve for the trabeculectomy + mitomycin C treated patients (group 1, continuous line) and the trabeculectomy treated patients (group 2, broken line). Cumulative probability of success (%) versus post-operative follow-up time (months)* (p = *0.0207*). (n, *number of patients).*

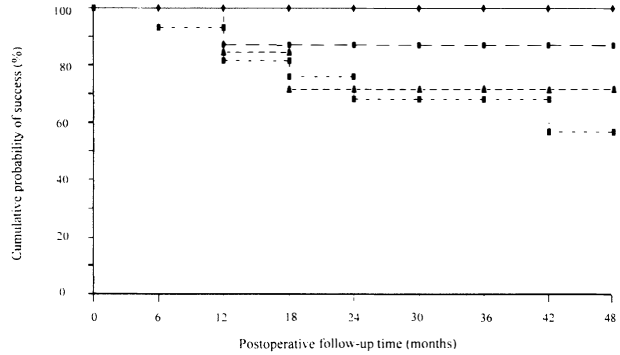

Fig. 2. *Survival curve for the four subgroups: trabeculectomy + MMC + 5-FU (continuous line); trabeculectomy + MMC (long broken line); trabeculectomy + 5-FU (medium broken line); trabeculectomy (short broken line). Cumulative probability of success (%) versus post-operative follow-up time (months)* (p = *0.0379*).

have been no reports that clarify whether OM enhances or predicts success of a filtering procedure. The duration of the response of eyes with successful filtering procedures to digital ocular pressure (DOP) was quantified.[22]

We give great importance to the lowering of the IOP after OM: the extent of the IOP decrease is related to scar formation and bleb efficacy. Cotton-tip focal massage of the filtration site deforms the edge of the trabeculectomy flap.[17] Early scar formation is broken by the misalignment of the flap edge and flow rate is increased via the larger bleb.[23] During the first post-operative days deforming the area of the scleral flap can benefit the outcome of filtering surgery in glaucoma.[24]

Our post-operative regimen did not include suture lysis. Undoubtedly, suture lysis following trabeculectomy has become an established procedure in the early post-operative period to titrate filtration. Sometimes, we use laser suture lysis in the management of failing filtering blebs. However, it is not considered an innocuous procedure. Complications have been widely reported[25–31] and may be observed in up to 30% of eyes

Table 5. *Surgical complications*

	Trabeculectomy with adjunctive mitomycin C (group 1)	Trabeculectomy (group 2)
	No. of eyes	No. of eyes
Early complications (< 3 months)		
Shallow anterior chamber	5	4
Choroidal effusions	3	2
Hyphaema	1	1
Anterior chamber inflammation	2	1
Corneal epithelial defect	4	5
Late complications (> 3 months)		
Bleb fibrosis	1	7[a]
Bleb leak	1	0
Hypotony maculopathy	1	0
Corneal epithelial defect	0	0
Scleral thinning	1	0
Progression of cataract	2	3
Endophthalmitis	0	0

[a]$p = 0.0026$, Fisher exact test.

undergoing this procedure.[32] In addition, the risk of persistent bleb leak and hypotony after argon laser suture lysis in patients undergoing trabeculectomy with MMC has to be strongly considered.[29–31] Also, in this study, the use of suture lysis could have increased bleb survival, especially in patients who did not receive intraoperative MMC, so we decided not to use it because during follow-up we did not know which patients had received intraoperative MMC. In fact, all patients were examined by a clinician who was masked to the treatment. Therefore the risk of developing bleb leak and hypotony could be too high in patients receiving the combination of MMC, suture lysis, OM and 5-FU.

We performed additional 5-FU treatment after OM. 5-FU injections were able to decrease IOP to levels lower than 22 mmHg in all the eyes with a positive response to OM (14 of 14 in the MMC group and 14 of 18 in the trabeculectomy group). In addition, intraoperative application of MMC increases the rate of eyes with a positive response to OM.

In the MMC group a lower post-operative IOP at 6 months, at 1 year and almost 2 years after surgery was detected compared with the trabeculectomy group. These results were statistically significant at all time intervals studied.

The ability of MMC to prevent scarring of the filtration bleb in high-risk glaucomatous eyes has been amply reported.[33–35] The effectiveness and safety of the addition of MMC in primary trabeculectomies was recently investigated.[36–38] In the paper by Kupin *et al.*[36] the doses tested (0.5 mg/ml for 3 and 5 min, respectively) increased the success rate by decreasing IOP and post-operative medications, but were associated with a high incidence of prolonged hypotony, especially in younger patients. Smith *et al.*[38] reported four bleb leaks in their series of 36 eyes receiving intraoperative MMC (200 μg/ml for 3–5 min) during primary trabeculectomy. In the largest series to date regarding the use of intraoperative MMC, Suñer *et al.*[39] reported the overall incidence of hypotony maculopathy as 1.3%. The incidence was higher (3.9%) in eyes undergoing primary filtering procedures. All cases of hypotony maculopathy occurred after significant events, including laser suture lysis (LSL) in most cases. In addition, Suñer *et al.* used the maximal accepted dosage of MMC (0.5 mg/ml for 5 min).

In our sample one patient in the MMC treated group (3.3%) developed hypotony maculopathy after bleb leak. The patient possessed two of the previously reported risk factors: he was much younger (51 years) than the other patients in the study and his refractive error was −6.50 dioptres. The sclera in young patients is more elastic and flexible than that of older patients, and may contract more in hypotony.[40] Then, myopic sclera is thinner, less rigid, and contracts during hypotony.[40]

Although further investigations are required to determine an optimal concentration of MMC to miminise the incidence of post-operative hypotony, Palmer[41] suggested that 0.2 mg/ml MMC is sufficiently dilute to be used for primary filtering procedures. Zacharia *et al.*[42] found that a longer exposure time to MMC markedly increased the risk of post-operative hypotony. Neelakantan *et al.*[43] reported a similar post-operative control of IOP with a significantly lower incidence of choroidal detachments using a concentration of 0.4 mg/ml for 3 min rather than 0.5 mg/ml for 5 min.

In our study we decided to minimise the risk of post-operative hypotony by using a 0.2 mg/ml concentration and a 3 min exposure; the sponge was then placed on the episclera before scleral flap dissection, because we believe that cutting the scleral flap before MMC application increases the risk of MMC entering the eye.

Intercurve analysis showed the best success rate in patients experiencing intraoperative MMC and post-operative 5-FU; no case of hypotony was found in this subgroup. This is not a surprising finding because these patients showed a worse IOP control during follow-up, so that OM and 5-FU injections were needed. According to Zacharia *et al.*,[42] MMC may be so much more potent than 5-FU that the addition of post-operative 5-FU treatment to an eye treated with MMC does not increase the likelihood of hypotony.

Visual acuity decreased in three eyes in the MMC group. In two of these the visual loss was linked to progression of cataract. In the other one hypotony maculopathy caused deterioration of visual acuity from 20/25 to 20/200; revision of the scleral flap resulted in restoration of visual acuity (20/25).

In the trabeculectomy group five patients lost two or more lines of visual acuity. Three patients had progression of cataract. After 6 months of follow-up one eye was considered a complete failure: the patient developed early choroidal detachment, the bleb failed and IOP was no longer controlled despite maximum medical therapy. After 6 months visual acuity was two lines below the pre-operative level.

Corneal epithelial defects appeared only in patients treated with 5-FU. In all such cases the epitheliopathy was resolved with lubrication therapy and there were no long-term complications.

The comparison of success rates between the subgroup receiving only post-operative 5-FU and the subgroup not receiving antimetabolite therapy confirms the impression of Hefetz *et al.*[16] that a delayed 5-FU regimen increases the success rate after trabeculectomy.

Although in our study the group receiving intraoperative MMC and post-operative 5-FU showed the best success rate and because, despite a common clinical experience, it is not proven that patients experiencing a rise in IOP after filtering surgery have a worse prognosis, the small number of patients and the lack of randomisation to post-operative 5-FU does not allow us to state definitively that intraoperative MMC + post-operative 5-FU ensure the most effective control of IOP.

The most encouraging data emerging from this study may be considered the effectiveness and relative safety of delayed post-operative 5-FU treatment in patients having clinical evidence of bleb failure in spite of intraoperative MMC.

The lowering of IOP after OM combined with 5-FU injections is likely to be associated with good control of IOP. The use of intraoperative MMC may ensure a better response to OM.

References

1. Heuer DK, Parrish RK II, Gressel MG, Hodapp E, Desjardins DC, Skuta GL, *et al*. 5-Fluorouracil and glaucoma filtering surgery. III. Intermediate follow-up of a pilot study. Ophthalmology 1986;93:1537–46.
2. Rockwood EJ, Parrish RK II, Heuer DK, Skuta GL, Hodapp E, Palmberg PF, *et al*. Glaucoma filtering surgery with 5-fluorouracil. Ophthalmology 1987;94:1071–8.
3. Weinreb RN. Adjusting the dose of 5-fluorouracil after filtration surgery to minimize side effects. Ophthalmology 1987;94:564–70.
4. Rabowsky JH, Ruderman JM. Low-dose 5-fluorouracil and glaucoma filtering surgery. Ophthalmic Surg 1989;20:347–9.
5. Ruderman JM, Welch DB, Smith MF, Shock DE. A randomized study of 5-fluorouracil and filtration surgery. Am J Ophthalmol 1987;104:218–24.
6. The Fluorouracil Filtering Surgery Study Group. Three-year follow-up of the Fluorouracil Filtering Surgery Study. Am J Ophthalmol 1993;115:82–92.
7. Liebmann JM, Ritch R, Marmor M, Nunez J, Wolner B. Initial 5-fluorouracil trabeculectomy in uncomplicated glaucoma. Ophthalmology 1991;98:1036–41.
8. Nakano Y, Araie M, Shirato S. Effect of postoperative subconjunctival 5-fluorouracil injections on the surgical outcome of trabeculectomy in the Japanese. Graefes Arch Clin Exp Ophthalmol 1989;227:569–74.
9. Ophir A, Ticho U. A randomized study of trabeculectomy and subconjunctival administration of fluorouracil in primary glaucomas. Arch Ophthalmol 1992;110:1072–5.
10. Ticho U, Ophir A. Late complications after glaucoma filtering surgery with adjunctive 5-fluorouracil. Am J Ophthalmol 1993;115:506–10.
11. Goldenfeld M, Krupin T, Ruderman JM, Wong PC, Rosenberg LF, Ritch R, *et al*. 5-Fluorouracil in initial trabeculectomy: a prospective, randomized, multicenter study. Ophthalmology 1994;101:1024–9.
12. Shapiro MS, Thoft RA, Friend J, Parrish RK, Gressel MG. 5-Fluorouracil toxicity to the ocular surface epithelium. Invest Ophthalmol Vis Sci 1985;26:580–3.
13. Knap A, Heuer DK, Stern GA, Driebe WT Jr. Serious corneal complications of glaucoma filtering surgery with postoperative 5-fluorouracil. Am J Ophthalmol 1987;103:183–7.
14. Lee DA, Hersh P, Kersten D, Melamed S. Complications of subconjunctival 5-fluorouracil following glaucoma filtration surgery. Ophthalmic Surg 1987;18:187–90.
15. Krug JH, Melamed S. Adjunctive use of delayed and adjustive low-dose 5-fluorouracil in refractory glaucoma. Am J Ophthalmol 1990;109:412–8.
16. Hefetz L, Keren T, Naveh N. Early and late postoperative application of 5-fluorouracil following trabeculectomy in refractory glaucoma. Ophthalmic Surg 1994;25:715–9.
17. Traverso CE, Greenidge KC, Spaeth GL, Wilson RP. Focal pressure: a new method to encourage filtration after trabeculectomy. Ophthalmic Surg 1984;15:62–5.
18. Fisher LD, Van Belle G. Biostatistics: a methodology for the health sciences. New York: Wiley, 1993;801–22.
19. Lee ET. Statistical methods for survival data analysis. Belmont, CA: Lifetime Learning Publications, 1980.
20. Lee E, Desu M. A computer program for comparing *k* samples with right-censored data. Comput Prog Biomed 1972;2:315–21.
21. Mattox C. Glaucoma filtration surgery and antimetabolites. Ophthalmic Surg Lasers 1995;26:473–80.
22. Kane H, Gaasterland DE, Monsour M. Response of filtered eyes to digital ocular pressure. Ophthalmology 1997;104:202–6.
23. Katz LJ, Spaeth GL. Filtration surgery. In: Ritch R, Shields MB, Krupin T, editors. The glaucomas, vol 1. St Louis: CV Mosby, 1989:653–96.
24. Spaeth GL. Needling versus medical treatment in encapsulated blebs: a randomized, prospective study [discussion]. Ophthalmology 1997;104:1220.
25. Savage JA, Condon GP, Lytle RA, Simmons RJ. Laser suture lysis after trabeculectomy. Ophthalmology 1988;95:1631–8.
26. Melamed S, Ashkenazi I, Glovinshi J, Blumenthal M. Tight scleral flap trabeculectomy with postoperative laser suture lysis. Am J Ophthalmol 1990;109:303–9.
27. DiSclafani M, Liebmann JM, Ritch R. Malignant glaucoma following argon laser release of scleral flap sutures after trabeculectomy. Am J Ophthalmol 1989;108:597–8.
28. Schwartz AL, Weiss HS. Bleb leak with hypotony after suture lysis and trabeculectomy with mitomycin C. Arch Ophthalmol 1992;110:1049.
29. Trope GE, Pavlin CJ, Bau A, Baumal CR, Foster FS. Malignant glaucoma: clinical and ultrasound biomicroscopic features. Ophthalmology 1994;101:1030–5.
30. Jampel HD, Pasquale LR, Dibernardo C. Hypotony maculopathy following trabeculectomy with mitomycin C. Arch Ophthalmol 1992;110:1049.
31. Kee C, Kaufman PL. Profound long-term hypotony without maculopathy after trabeculectomy with antimetabolite. Acta Ophthalmol (Copenh) 1994;72:388–90.
32. Macken P, Buys Y, Trope GE. Glaucoma laser suture lysis. Br J Ophthalmol 1996;80:398–401.
33. Kitazawa Y, Kawase K, Matsushita H, Minobe M. Trabeculectomy with mitomycin: a comparative study with fluorouracil. Arch Ophthalmol 1991;109:1693–8.
34. Skuta GL, Beeson CC, Higginbotham EJ, Lichter PR, Musch DC, Bergstrom TJ, *et al*. Intraoperative mitomycin versus postoperative 5-fluorouracil in high-risk glaucoma filtering surgery. Ophthalmology 1992;99:438–44.
35. Katz GJ, Higginbotham EJ, Lichter PR, Skuta GL, Musch DC, Bergstrom TJ, Johnson AT. Mitomycin C versus 5-fluorouracil in high-risk glaucoma filtering surgery: extended follow-up. Ophthalmology 1995;102:1263–9.
36. Kupin TH, Juzych MS, Shin DH, Khatana AK, Olivier MMG. Adjunctive mitomycin-C in primary trabeculectomy in phakic eyes. Am J Ophthalmol 1995;119:30–9.
37. Mirza GE, Karakucuk S, Dogan H, Erkilic K. Filtering surgery with mitomycin-C in uncomplicated (primary open angle) glaucoma. Acta Ophthalmol (Copenh) 1994;72:155–61.
38. Smith MF, Doyle JW, Nguyen QH, Sherwood MB. Results of intraoperative 5-fluorouracil or lower dose mitomycin-C administration on initial trabeculectomy surgery. J Glaucoma 1997;6:104–10.
39. Suñer IJ, Greenfield DS, Miller MP, Texeira Nicolela M, Palmberg PF. Hypotony maculopathy after filtering surgery with mitomycin C. Ophthalmology 1997;104:207–14.
40. Gass JDM. Hypotony maculopathy. In: Bellows JG, editor. Contemporary ophthalmology. Honoring Sir Stewart Duke-Elder. Baltimore: Williams & Wilkins, 1972:chap.34.
41. Palmer SS. Mitomycin as adjunct chemotherapy with trabeculectomy. Ophthalmology 1991;98:317–21.
42. Zacharia PT, Deppermann SR, Schuman JS. Ocular hypotony after trabeculectomy with mitomycin C. Am J Ophthalmol 1993;116:314-26.
43. Neelakantan A, Rao BS, Vijaya L, Grandham SB, Krishnan N, Priya S, Murugeshan R. Effect of the concentration and duration of application of mitomycin-C in trabeculectomy. Ophthalmic Surg 1994;25:612–5.