Trabeculectomy augmented with mitomycin C application under the scleral flap

S Beatty, T Potamitis, S Kheterpal, E C O'Neill

Abstract

***Aim*—The authors investigated the safety and intraocular pressure (IOP) lowering effectiveness of trabeculectomy augmented with mitomycin C application beneath the scleral flap, and assessed the influence of preoperative risk factors on the surgical outcome.**

***Methods*—A retrospective study of 72 consecutive high risk eyes undergoing trabeculectomy with adjunctive mitomycin C (0.2 mg/ml) applied under the scleral flap for 5 minutes was performed. Each eye was ascribed a score based on the number of preoperative risk factors, and categorised into one of three risk factor groups. Success was described as unqualified where IOP was ≤ 21 mm Hg without medication and qualified where antiglaucomatous therapy was required to maintain it at such a level. A life table analysis of IOP control was calculated.**

***Results*—The mean IOP (SD) fell from a preoperative level of 28.4 (6.9) to a level of 16.63 (8.06) mm Hg at the last follow up (paired Student's *t* test: p< 0.0001). Fifty two eyes (72%) were classed as unqualified successes. The survival rates did not differ significantly between different risk factor groups (log rank test: χ^2 = 0.967, p>0.1). The incidence of postoperative complications compared favourably with reports of mitomycin C application between Tenon's capsule and the undissected scleral bed.**

***Conclusion*—The results illustrate that mitomycin C applied beneath the scleral flap during trabeculectomy in high risk eyes is associated with a success rate comparable to other modes of application. The incidence of potentially serious complications such as conjunctival wound leak and prolonged hypotony was lower than previously published data reporting sub-Tenon's administration of mitomycin C. The number and nature of preoperative risk factors do not appear to influence the surgical outcome. A possible mechanism of action is proposed.**

(*Br J Ophthalmol* 1998;**82**:397–403)

Birmingham and Midland Eye Centre, City Hospital NHS Trust, Dudley Road, Birmingham B18 7QU
S Beatty
T Potamitis
S Kheterpal
E C O'Neill

Correspondence to:
Mr S Beatty.

Accepted for publication
6 November 1997

Scarring at the surgical site is the most common cause of failure of glaucoma filtering surgery.[1 2] Fibroblasts play a critical role in the healing process and agents which inhibit their proliferation have been introduced to modulate tissue reaction after fistulising surgery.[3–6] Mitomycin C (MMC) is one such agent which has been shown to successfully prolong the surgical results after trabeculectomy in both high risk and uncomplicated glaucoma.[7–14]

The optimum regimen of MMC administration has yet to be established. However, it is known that this antiproliferative agent acts in a dose and time dependent way.[15] It may therefore be postulated that the surgical outcome will depend on preoperative risk factors when the dosage and duration of exposure of MMC is constant.

The appropriate site of MMC administration is also a matter of considerable debate, the vast majority of published data reporting its application between the undissected scleral bed and the overlying Tenon's capsule. In an attempt to reduce the risk of ocular surface complications we apply the antimetabolite beneath the scleral flap only. This study represents the largest series of trabeculectomies augmented with MMC application to this site. The safety and efficacy of this procedure was evaluated and the influence of known preoperative risk factors on the surgical outcome was assessed.

Patients and methods

We reviewed the records of 69 consecutive patients (72 eyes) who underwent MMC augmented trabeculectomy for medically uncontrolled glaucoma between August 1992 and June 1995 and who had at least 6 months' postoperative follow up. All operations were performed at the Birmingham and Midland Eye Hospital by one specialist glaucoma surgeon (EO'N), or an ophthalmologist in training under his direct supervision.

Data retrieved for each operated eye may be divided into preoperative, intraoperative, and postoperative. Preoperative information gathered included patient's age, sex, race, previous surgical procedures, number of glaucomatous medications, last recorded intraocular pressure (IOP), ocular comorbidity, and best corrected visual acuity (VA). Intraoperative data included the grade of operating surgeon and the surgical technique used. Postoperatively IOP and visual acuity measurements were recorded 1 day, 2 weeks, 3 months, 6 months, and 1 year following surgery, and at the last available follow up. Complications were also noted, with particular attention directed to the diagnosis of conjunctival wound leak, shallow anterior chamber (AC), flat AC, prolonged hypotony (IOP < 5 mm Hg for more than 2 weeks), choroidal detachment, corneal epithelial defects, and superficial punctate keratitis (SPK).

In order to classify eyes in terms of preoperative risk we established a "cumulative risk factor index" (CRFI) before the collection of data.

Table 1 The cumulative risk factor index (CRFI): preoperative characteristics known to have an adverse effect on the surgical outcome of filtration surgery were each ascribed a score and the total calculated

Preoperative characteristic	*Score*
Black race	1
Previous incisional ocular surgery	1
⩾ 2 topical medications for ⩾ 18 months	1
30 years ⩽ age ⩽ 50 years	1
Age ⩽ 30 years	2
Complicated glaucoma*	1

*Complicated glaucoma = any glaucoma other than primary open and capsulare types.
Risk factor (RF) group A = 1–2 points, RF group B = 3–4 points, RF group C = 5–6 points.

Ocular and systemic patient characteristics shown to have an adverse effect on the outcome of trabeculectomy by previous investigators were each ascribed a score (Table 1), and the total calculated. These included a history of previous incisional ocular surgery involving the superior conjunctiva,[16–19] prolonged topical antiglaucomatous medication,[20 21] "complicated glaucoma" (any glaucoma other than primary open angle glaucoma and glaucoma capsulare),[22–33] black race,[34–36] and young eyes (<50 years).[16 37–40] We ascribed a score of 2 for eyes aged less than 30 years as they are associated with a success rate approximately half that of eyes aged between 30 and 49 years.[39] Eyes achieving a CRFI count of 1 to 2 were classed in risk factor (RF) group A, CRFI counts of 3 to 4 were classed in RF group B, and scores of 5 to 6 in RF group C.

Sixteen patients underwent trabeculectomy with adjunctive MMC in one eye and conventional filtration surgery in the fellow eye. At the time of the surgical procedures, fellow eyes were perfect matches in terms of preoperative risk including age (plus or minus 2 years), race, number and nature of previous incisional ocular procedures, and topical treatment. In terms of antiglaucoma medication paired eyes received the same type (β blocker with or without pilocarpine) and brand of drops for a comparable period of time (4–5 years) before surgery. Furthermore, all operations in this group were performed by one surgeon (EO'N). The surgical outcomes of the two surgical techniques were compared for these 32 paired eyes.

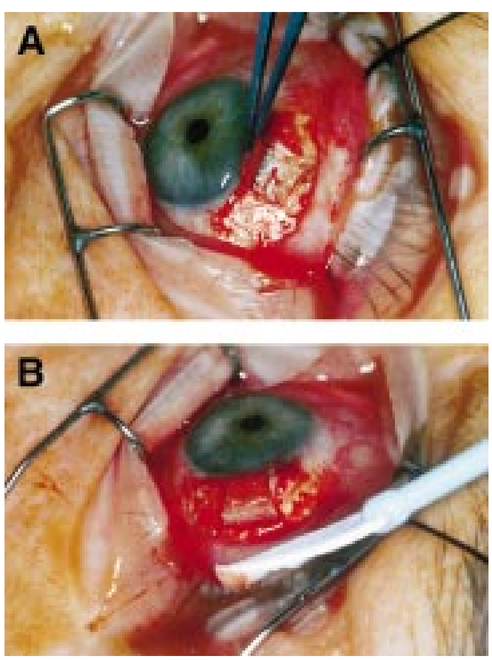

Figure 1 (A) Following the creation of a fornix based conjunctival flap, a partial thickness rectangular scleral flap is dissected. (B) A trimmed, MMC saturated sponge is then placed beneath the scleral flap while taking care that it does not come into contact with the conjunctiva.

Table 2 Characteristics of patients undergoing MMC augmented trabeculectomy*

Variable	*No (%)*
Race	
Black	43 (62.5)
Asian	4 (5.5)
White	22 (32)
Sex	
Male	31 (45)
Female	38 (55)
Glaucoma diagnosis	
Primary open angle	54 (75)
Glaucoma capsulare	4 (5.6)
Normal tension	4 (5.6)
Uveitic	6 (8.5)
Angle closure	1 (1.3)
Neovascular	1 (1.3)
Congenital	2 (2.7)

*Age range of the patients was 8–83 years (mean 64.3 (SD 11) years).

Before the collection of data successful IOP control was defined as unqualified where IOP was ⩽ 21 mm Hg without medication and qualified where antiglaucomatous therapy was required to maintain it at such a level. In cases of low tension glaucoma the procedure was considered to be an unqualified success where IOP was reduced by at least 30% of the preoperative level without ocular hypotensives, and qualified if drugs were required to achieve this level of IOP reduction. Eyes with a postoperative intraocular pressure ⩾21 mm Hg and ⩽24 mm Hg were classed as qualified failures, and where IOP was ⩾25 mm Hg the surgery was considered to have failed completely.

Statistical comparisons between groups were performed using the Student's *t* test, median test, or ANOVA for quantitative data. Categorical data were compared using the χ^2 test, or McNemar's test when paired eyes were being considered. The probability of success at various times in the postoperative period was calculated by Kaplan–Meier life table analysis and survival curves were drawn. Intercurve analysis was performed using the log rank test, and the influence of risk factors on survival was estimated using the Cox regression proportional hazards model in combination with joint significance tests.

Table 3 Previous surgical procedures among 41 eyes undergoing MMC augmented trabeculectomy

Previous surgical procedure	*No (%)*
Trabeculectomy (one)	17 (23.5)
Trabeculectomies (two)	10 (13.8)
Trabeculectomies (three)	1 (1.4)
ECCE	7 (9.7)
ECCE + trabeculectomy (combined)	1 (1.4)
ICCE	1 (1.4)
Peripheral iridectomy	2 (2.8)
Goniotomy	1 (1.4)
Retinal detachment repair	1 (1.4)

ECCE = extracapsular cataract extraction; ICCE = intracapsular cataract extraction.

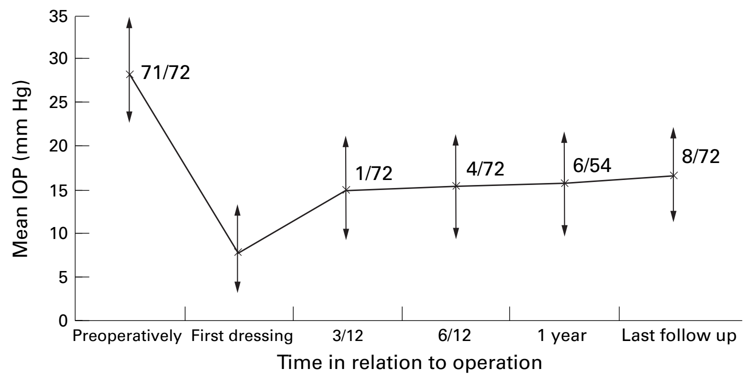

Figure 2 Intraocular pressure effect of trabeculectomy with adjunctive mitomycin C for 72 high risk eyes. Numbers above the line show the fraction of patients receiving antiglaucoma medication.

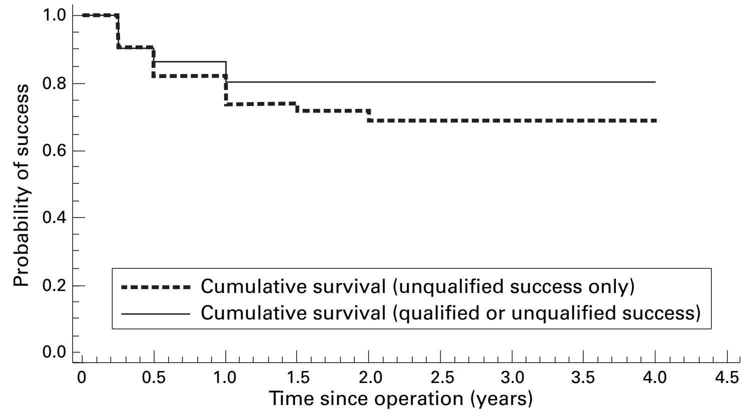

Figure 3 Kaplan–Meier cumulative survival plot for trabeculectomies augmented with mitomycin C application beneath the scleral flap.

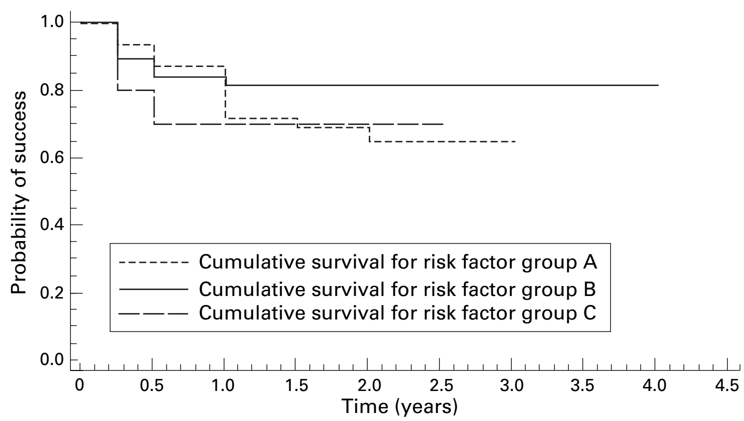

Figure 4 Kaplan–Meier cumulative survival plot for mitomycin augmented trabeculectomies according to risk factor category.

SURGICAL TECHNIQUE

A fornix based conjunctival flap was dissected and a partial thickness 2 × 3 mm rectangular scleral flap created (Fig 1A). For the application of MMC, a 2 × 2 mm cellulose sponge (Surgi, Eschenburg, Germany) saturated with 0.2 mg/ml solution of MMC (Kyowa, Hako, London) was applied under the scleral flap for 3 minutes and then a freshly saturated sponge was applied for a further 2 minutes (Fig 1B). The conjunctiva was held back with a forceps during application of the MMC, and was not draped over the sponge at any stage, in order to protect it from contact with the antimetabolite. The surgical site was then irrigated with 10 ml of balanced salt solution. Only then was the anterior chamber entered, a clear cornea paracentesis performed, and a fistula beneath the scleral flap created. A peripheral iridectomy was performed in all cases. The scleral flap was sutured with two interrupted 10-0 nylon sutures (Ethicon, Somerville, NJ, USA) with slightly greater tension than a standard trabeculectomy, taking care to maintain anterior chamber depth and prevent overfiltration. Tenon's capsule and the conjunctiva were closed in a single layer with 8-0 Vicryl (Ethicon, Somerville, NJ, USA).

Following surgery, all eyes received a standard regimen of topical atropine (1% twice daily) and corticosteroid-antibiotic preparation (Betnesol-N, Evans Medical, Horsham, Sussex) four times daily. In no case was argon suture lysis or ocular massage performed postoperatively.

Results

Seventy two eyes of 69 patients which underwent MMC augmented trabeculectomy with at least 6 months' follow up were identified. Patient characteristics are listed in Table 2. Mean follow up time was 18.3 months (range 6–48 months). Forty one eyes (56.9%) had undergone previous incisional ocular procedures (Table 3). All cataract extractions were performed through a limbal section. Almost all operated eyes (98.6%) had received chronic topical medical therapy for a duration of 2–5 years. Of these, all had been exposed to the combination of a β blocker and pilocarpine for 18 months or more. Adrenaline based products were not used in any case for more than 5 months before surgery. No eye in the study group had been exposed to the mixture of adrenaline and guanethidine monosulphate (Ganda). The cumulative risk factor (RF) index categorises 30 eyes in RF group A, 36 eyes in RF group B, and six eyes in RF group C.

The mean preoperative IOP (SD) was 28.4 (6.9) mm Hg. Three months postoperatively the mean IOP was significantly lower at 15.04 (5.83) mm Hg (paired Student's *t* test: $p<0.0001$). At the time of last follow up the average IOP was 16.63 (8.06) mm Hg ($p<0.0001$), representing a mean reduction of 41.4%. The IOP was reduced by more than 50% in 31 eyes (43%) and by over 30% in 55 eyes (77.7%). Mean IOP did not change significantly after the third postoperative month (Fig 2) and the drop in IOP did not differ significantly between cumulative risk factor groups (ANOVA: $F = 0.56$, $p > 0.05$).

The overall success rate was 83.3% (60 eyes) at last follow up. Of these, eight (11.1%) required topical antiglaucomatous medications to maintain IOP ≤21 mm Hg and 52 (72%) were unqualified successes. Twelve MMC augmented trabeculectomies (16.66%) were classed as failures. Of these, eight (66.6%) failed within the first three postoperative months and 10 (83.3%) by the sixth postoperative month.

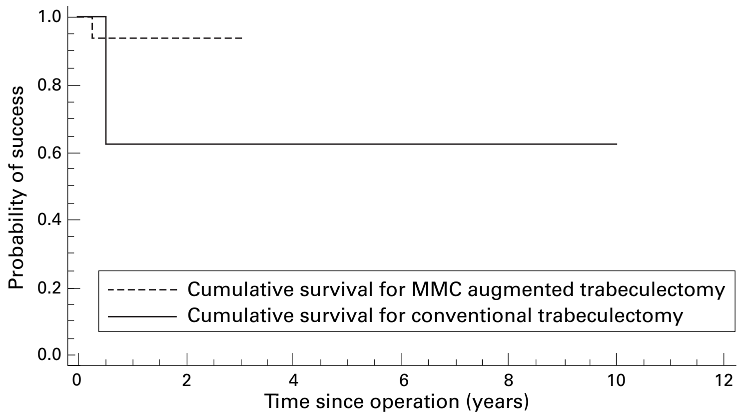

Figure 5 Kaplan–Meier cumulative survival plot for conventional and mitomycin C (MMC) augmented trabeculectomies in paired eyes.

Table 4 Postoperative complications for 72 eyes undergoing trabeculectomy with mitomycin C

Complication	*No (%)*
Corneal abrasion	0 (0)
SPK	0 (0)
Dellen	2 (2.8)
Chronic wound leak	2 (2.8)
Shallow AC	6 (8.3)
Hyphaema	5 (6.9)
Intense uveitis	1 (1.4)
Choroidal detachment	3 (4.2)
Prolonged hypotony	1 (1.4)
Hypotonous maculopathy	0 (0)
Encysted bleb	6 (8.3)
Endophthalmitis	1 (1.4)
Aqueous misdirection	0 (0)

AC = anterior chamber; SPK = superficial punctate keratitis.

The probability of complete or qualified success during postoperative follow up for all MMC augmented trabeculectomies is presented in the Kaplan–Meier survival analysis curves (Fig 3). The survival rates did not differ significantly between the three cumulative RF groups 1 year postoperatively (log rank test: p>0.1) or at the time of the last assessment (p>0.1) (Fig 4).

Using stepwise variable selection of a Cox regression proportional hazards model we investigated the influence of individual risk factors on the survival of MMC augmented trabeculectomy. The risk of failure was unaffected by race (p = 0.21), a history of previous incisional ocular surgery (p = 0.96), glaucoma type (p = 0.06), or age category (p = 0.84). Joint significance tests (Wald test and likelihood ratio) failed to establish a significant relation between any combination of risk factors and survival (p > 0.1). However, the adverse effect of complicated glaucoma in association with Afro-Caribbean race did approach statistical significance (Wald test: p = 0.09; likelihood ratio: p = 0.06).

Sixteen patients in the study group underwent trabeculectomy with adjunctive MMC in one eye and conventional filtration surgery in the fellow eye. Of these, all paired eyes were perfectly matched in terms of preoperative risk factors for failure. Follow up was longer for eyes undergoing conventional trabeculectomy (mean 37 months; range 8–61 months) than their fellow eyes (mean 20 months; range 6–27 months). Of the 16 eyes in this group undergoing filtration surgery with adjunctive MMC, unqualified success was seen in 12 (75%) compared with four (25%) of those undergoing conventional filtration surgery (McNemar's test: χ^2 = 10.54, p<0.001). All eyes where intraoperative MMC was used were classed as either qualified or unqualified successes, compared with only nine (56.25%) of their fellow eyes undergoing conventional trabeculectomy (McNemar's test: χ^2 = 5.14, p<0.05). Cumulative success probability for the two surgical techniques was calculated using Kaplan–Meier life table analysis, and survival curves drawn (Fig 5). Intercurve analysis revealed that eyes undergoing conventional trabeculectomy were at increased risk of failure compared with their fellow eyes where adjunctive MMC was used (log rank test: χ^2 = 3.85, p<0.05).

Postoperative complications of all 69 patients who underwent trabeculectomy with intraoperative MMC are shown in Table 4. All cases of shallow anterior chamber, wound leakage, prolonged hypotony, or choroidal detachment resolved spontaneously. Six blebs were described as encysted in the postoperative period; however, the IOP was well controlled without medication in four of these. The case of intense postoperative uveitis occurred in an eye with glaucoma secondary to Fuchs' heterochromic cyclitis. One case of late onset low grade postoperative endophthalmitis was recorded.

Visual acuity at the time of the last assessment was improved or unchanged in 59 eyes (80%) and within 1 Snellen line of baseline in 66 eyes (91.6%). A decrease in visual acuity of 2 or more lines was seen in six eyes (8.3%) and a visual reduction of 3 or more lines was not experienced by any patient. The causes of significantly reduced visual acuity included the development of band keratopathy secondary to uveitis (one eye), end stage glaucoma with total field loss (one eye), and progression of lens opacities (four eyes). None of the patients with decreased acuity was observed to have had prolonged hypotony.

Discussion

Trabeculectomy, first introduced by Cairns[41] in 1967 and later modified by Watson,[42] has become the accepted method of surgical treatment of various types of glaucoma. The larger series report an overall success rate (IOP ⩽ 21 mm Hg with or without medication) of between 86% and 90%,[18 19] with 71.9% achieving unqualified success.[19] However, those studies include few high risk eyes.

Many factors are associated with increased risk of failure after glaucoma filtration surgery. These include prolonged prior topical antiglaucomatous medication,[20 21] young eyes,[16 37–40] previous intraocular surgery,[16–19] aphakia,[24–26] uveitis,[27–29] rubeosis iridis,[30 31] angle recession,[32] angle closure glaucoma,[23 33] and black race.[34–36]

The first report of glaucoma surgery with adjunctive MMC was by Chen in 1983.[43] Many studies have since confirmed the enhanced the IOP lowering effectiveness of trabeculectomy augmented with sub-Tenon's MMC,[7 10–14 44 46–48] and a few investigators have reported its application to both sites (under and over the scleral flap).[8 9 45 49] To our knowledge there has only been one published account of filtration surgery augmented solely with intrascleral administration of MMC.[50] However, that study consisted of 12 eyes only and the surgical technique used differed from that reported here in that the conjunctival/Tenon's fascia was draped over the sponge at the time of antimetabolite application.[50]

In our series the mean IOP at last follow up was 16.63 (8.06) mm Hg, representing a mean reduction of 41.4% from preoperative IOP and an unqualified success rate of 72%. Previous investigators using the same regimen (0.2 mg/ml MMC for a duration of 5 minutes) but applying the antimetabolite under the conjunctival flap and over the undissected scleral bed have reported final IOP between 9.9 mm Hg and 13.1 mm Hg, IOP reductions between 58.5% and 59.9%, and complete IOP control in 72% to 81.8% of cases.[10 12 51] However, comparisons must be made with caution as the procedure was performed as an initial surgery in primary open angle glaucoma in one of these reports,[12] and the longest follow up was only 6 months in another.[10] Using our criteria for IOP control, and without regard to the regimen used or to preoperative risk factors, the literature reports unqualified success in 43.3%–94.8% of operated eyes following sub-Tenon's application of MMC,[11 13 46–48 51 52] 18.2% for intrascleral MMC administration[50] and 70%–86.2% where MMC is applied to both sites.[8 9 45 49] We found that the risk of failure is significantly reduced after the first six postoperative months, an observation also made in cases of conventional filtration surgery.[22 33]

Survival rates were similar for different cumulative risk factor groups, and no associations between failure and specific risk factors were found. These results indicate that the success rates following MMC augmented trabeculectomy using our regimen are independent of the number and nature of preoperative adverse prognostic indicators.

The best study design for evaluating the benefits of MMC augmentation of trabeculectomy is to compare the surgical outcomes between fellow eyes following bilateral fistulising surgery, where only one eye received intraoperative MMC. In such a setting paired eyes share an identical background with respect to race, age, sex, type of glaucoma, operating surgeon, and preoperative risk factors. In this group of patients we found that MMC trabeculectomy was associated with a significantly higher incidence of qualified and/or unqualified success, and a greater probability of survival, than conventional filtration surgery.

Final postoperative visual acuity was unchanged or improved in 80% of operated eyes, comparing favourably with reports in the literature of MMC application under (72%)[50] or over (71.8%–86.7%)[11 32 52] the scleral flap, or to both sites (47%–79.3%).[8 45 49] In our study a reduction in visual acuity of more than 2 Snellen lines was not observed in any case and this compares with 0%–17.2% for studies exposing the same site to antimetabolite[45 49] and 5%–30% where the agent was placed between the scleral and conjunctiva.[7 13 46 47] No case of hypotonous maculopathy was observed in our patients and this may account for the low incidence of postoperative visual deterioration as this complication has contributed significantly to poor visual outcomes in previous studies.[13 47 49]

Postoperative complications were also examined in this study. Our incidence of ocular surface complications compare favourably with previously published data (corneal abrasions: 0%–18%[7 11 12 46 47 52]; SPK: 0%–5%,[8 9 11 45 46 49]; conjunctival wound leak: 0%–15%[7–13 32 45–47 49 51 52]). We believe that the relatively low incidence of postoperative conjunctival and corneal complications seen in this study reflects our surgical technique. We placed the soaked sponge under the dissected scleral flap so that the scleral bed and the posterior surface of the half thickness scleral flap were the only tissue planes in contact with MMC (Fig 1B). In contrast with previous studies, including those using the same site of application as we did, the conjunctival flap was not draped over the sponge.[8 9 45 49 50] Tenon's capsule and the cornea were therefore protected from direct exposure to, and overflow of, the antimetabolite.

The incidence of prolonged hypotony and hypotonous maculopathy following MMC augmented trabeculectomy varies from 0% to 65% and 0% to 18% respectively.[7–12 45–54] Our results compare favourably with most previous studies for these and other complications associated with hypotony such as choroidal detachment (5%–43%[7 8 10–13 43 46 47 50 53]), shallow AC (10%–45%[11 12 46 49]), and cataract progression (5%–48%[7 8 11–13 46 49]). We believe the low incidence of these complications in the current study also reflects our surgical technique.

Mitomycin C is detectable in human aqueous humour within minutes after external application to sclera, and higher concentrations have been associated with scleral than with episcleral application.[55] This gives cause for concern for a more intense anterior chamber reaction following surgery, and possible toxic effects on the corneal endothelium, when our technique is used.[56 57] However, complete disappearance of MMC from the AC within 6 hours of its application has been demonstrated in rabbit eyes.[56] In our study only one case (1.3%) of intense postoperative uveitis was noted (in a patient with glaucoma secondary to Fuchs' heterochromic cyclitis) and this compares favourably with reports in the literature (5%–5.3%[7 55]).

Trabeculectomy augmented with MMC is known to be associated with a high incidence of encapsulated blebs postoperatively and this is thought to reflect the alteration of fibroblast activity in favour of Tenon's cyst (TC) formation.[58] Histopathologically, a TC is an avascular subconjunctival membrane of fibrous connective tissue with an acellular internal lining.[59] The site of application may therefore be expected to play a role. However, this is not reflected in the literature with an incidence of 2%–15% where the sponge is placed between the sclera and Tenon's capsule,[7 49 51 52] no cases reported for intrascleral MMC application,[50] and between 0% and 29% for studies reporting on its administration to both sites.[8 9 49 59] Six eyes (8.3%) in the current series developed encapsulated blebs. Of these, four (66%) were classed as unqualified successes, in keeping with previous reports.[59]

Filtration surgery with adjunctive antimetabolite is associated with a higher risk of endophthalmitis (0%–5%[7–9 32 48 49 51]) than conventional fistulising surgery (0%–0.44%[22 23 60]). This may reflect the preponderance of thin walled blebs following this procedure.[61] One patient (1.4%) in the present study developed endophthalmitis postoperatively. Anaerobic diphtheroids were grown on culture of the vitreous fluid and the condition responded to topical and intravitreal (ceftazidine 2 mg in 0.1 ml and vancomycin 1 mg in 0.05 ml) antibiotics, resulting in a quiet eye and a final visual acuity of 6/9.

The mechanism of action of MMC in improving surgical outcomes following filtration surgery is still a matter of considerable debate. Failed and functioning blebs both have normal subepithelial connective tissue, but it is thicker and more dense in those that are non-filtering.[1] Subconjunctival fibroblasts are critical to the production of new extracellular matrix (collagen and glycosaminoglycans) in response to surgery.[62] Mitomycin C inhibits the proliferation of these fibroblasts.[15 63] Histopathological studies in rabbits, monkeys, and humans have shown that MMC creates a filtration site with hypocellular and acellular bleb cavities.[14 64 65] Therefore, the administration of MMC between Tenon's capsule and the undissected scleral bed would appear to be the logical site of application if surgical success rates are to be enhanced. It may be that irrigation of the surgical site following application of the antimetabolite under the scleral flap flushes sufficient amounts of the agent into the subconjunctival space to inhibit fibroblast proliferation.

However, MMC is known to modulate other mechanisms of wound healing such as collagen synthesis and fibroblast migration.[62 66 67] Moreover, there is evidence that subconjunctival fibroblast activity is influenced by other ocular components such as aqueous humour.[62] Aqueous has been shown to have a degenerative effect on collagen[68] and an inhibitory effect on sub-Tenon's capsule tissue proliferation.[69 70] It is possible therefore that application of MMC under the scleral flap modulates healing at the edges of the dissected flap. Consequently, more aqueous arrives at the subepithelial space in the postoperative period and impairs healing through its antiproliferative properties. This hypothesis is supported by findings in animals that MMC concentrations, even in tissues where it has been applied, fall below the minimum effective antiproliferative concentration within a few days of surgery and that its effects last much longer that tissue concentrations suggest.[56 71]

In conclusion, the results of this study illustrate that MMC applied under the scleral flap increases the success rate of filtration surgery in high risk eyes and is associated with a lower incidence of postoperative complications than reports of sub-Tenon's administration. The number and nature of preoperative risk factors do not appear to influence the surgical outcome. Further studies into the mechanism of action of this antiproliferative agent are necessary if the optimum dosage, duration of exposure, and site of application of MMC in filtration surgery are to be established.

1 Addicks EM, Quigley HA, Green WR, *et al*. Histologic characteristics of filtering blebs in glaucomatous eyes. *Arch Ophthalmol* 1983;**101**:795–8.
2 Hitchings RA, Grierson I. Clinico-pathological correlation in eyes with failed fistulising surgery. *Trans Ophthalmol Soc UK* 1983;**103**:84–8.
3 Skuta GL, Parish RK II. Wound healing in glaucoma filtering surgery. *Surv Ophthalmol* 1987;**32**:149–70.
4 Maumenee AE. External filtering surgery for glaucoma: the mechanism of function and failure. *Trans Am Ophthalmol Soc* 1960;**58**:319–28.
5 Teng CC, Chi HH, Katzin HM. Histology and mechanism of filtering operations. *Am J Ophthalmol* 1959;**47**:16–34.
6 Herschler J, Claflin AJ, Fiorentino G. The effect of aqueous humor on the growth of subconjunctival fibroblasts in tissue culture and its implications for glaucoma surgery. *Am J Ophthalmol* 1980;**89**:245–9.
7 Katz GJ, Higginbotham EJ, Lichter PR, *et al*. Mitomycin C versus 5-fluorouracil in high-risk glaucoma filtering surgery. *Ophthalmology* 1995;**102**:1263–9.
8 Mirza GE, Karakucuk S, Dogan H, *et al*. Filtering surgery with mitomycin C in uncomplicated (primary open angle) glaucoma. *Acta Ophthalmol* 1994;**72**:155–61.
9 Munden PM, Alward WLM. Combined phacoemulsification, posterior chamber intraocular lens implantation, and trabeculectomy with mitomycin C. *Am J Ophthalmol* 1995; **119**:20–9.
10 Mietz H, Krieglstein GK. Mitomycin C for trabeculectomy in complicated glaucoma: preliminary results after 6 months. *Ger J Ophthalmol* 1994;**3**:164–7.
11 Costa VP, Moster MR, Wilson RP, *et al*. Effects of topical mitomycin C on primary trabeculectomies and combined procedures. *Br J Ophthalmol* 1993;**77**:693–7.
12 Kitazawa Y, Suemori-Matsushita H, Yamamoto T, *et al*. Low-dose and high-dose mitomycin trabeculectomy as an initial surgery in primary open angle glaucoma. *Ophthalmology* 1993;**100**:1625–8.
13 Kupin TH, Juzych MS, Shin DH, *et al*. Adjunctive mitomycin C in primary trabeculectomy in phakic eyes. *Am J Ophthalmol* 1995;**119**:30–9.
14 Pasquale LR, Thibault D, Dorman-Pease ME, *et al*. Effect of topical mitomycin C on glaucoma filtration surgery in monkeys. *Ophthalmology* 1992;**99**:14–18.
15 Yamamoto T, Varani J, Soong HK, *et al*. Effects of 5-fluorouracil and mitomycin C on cultured rabbit subconjunctival fibroblasts. *Ophthalmology* 1990;**97**:1202–10.
16 Inaba Z. Long-term results of trabeculectomy in the Japanese: an analysis by life-table method. *Jpn J Ophthalmol* 1982;**26**:361–73.
17 Shirato S, Kitazawa Y, Mishima S. A critical analysis of the trabeculectomy results by a prospective follow-up design. *Jpn J Ophthalmol* 1982;**26**:468–80.
18 Schwartz AL, Anderson DR. Trabecular surgery. *Arch Ophthalmol* 1974;**92**:134–8.
19 Khaw PT, Tsai JC, Constable PH, *et al*. Preventing scarring after glaucoma filtration surgery with single application agents: a practical approach. *Asia-Pacific J Ophthalmol* 1995;**7**:6–13.
20 Lavin MJ, Wormald RPL, Migdal CS, *et al*. The influence of prior therapy on the success of trabeculectomy. *Arch Ophthalmol* 1990;**108**:1543–8.
21 Broadway D, Grierson I, Hitchings R. Adverse effects of topical antiglaucomatous medications on the conjunctiva. *Br J Ophthalmol* 1993;**77**:590–6.
22 Mills KB. Trabeculectomy: a retrospective long-term follow up of 444 cases. *Br J Ophthalmol* 1981;**65**:790–5.
23 Watson PG, Jakeman C, Ozturk M, *et al*. The complications of trabeculectomy (a 20- year follow-up). *Eye* 1990;**4**:425–38.
24 Heuer DK, Gressel MG, Parrish RK II, *et al*. Trabeculectomy in aphakic eyes. *Ophthalmology* 1984;**91**:1045–51.
25 Herschler J. Medically uncontrolled glaucoma in aphakia and pseudophakia (Editorial). *Ann Ophthalmol* 1981;**13**: 909.
26 Tomey KF, Traverso CE. The glaucomas in aphakia and pseudophakia. *Surv Ophthalmol* 1991;**36**:79–112.
27 Hoskins HD, Hetherington J Jr, Shaffer RN. Surgical management of the inflammatory glaucomas. *Perspect Ophthalmol* 1977;**1**:173–81.
28 Kanski JJ, McCallister JA. Trabeculodialysis for inflammatory glaucoma in children and young adults. *Ophthalmology* 1985;**92**:927–30.
29 Jones NP. Glaucoma in Fuchs' heterochromic uveitis: aetiology, management and outcome. *Eye* 1991;**5**:662–7.

30 Allen RC, Bellows AR, Hutchinson BT, *et al*. Filtration surgery in the treatment of neovascular glaucoma. *Ophthalmology* 1982;**89**:1181–7.
31 Katz LJ, Spaeth GL. Surgical management of the secondary glaucomas: part I. *Ophthalmic Surg* 1987;**18**:826–84.
32 Mermoud A, Salmon JF, Straker C, *et al*. Post-traumatic angle recession glaucoma: a risk factor for bleb failure after trabeculectomy. *Br J Ophthalmol* 1993;**77**:631–4.
33 Ridgeway AEA. Trabeculectomy—a follow up study. *Br J Ophthalmol* 1974;**58**:680–6.
34 Miller RD, Barber JC. Trabeculectomy in black patients. *Ophthalmic Surg* 1981;**12**:46–50.
35 Wilson MR. Posterior lip sclerectomy vs trabeculectomy in West Indian blacks. *Arch Ophthalmol* 1989;**107**:1604–8.
36 Merritt JC. Filtering procedues in American blacks. *Ophthalmic Surg* 1980;**11**:91–4.
37 Beauchamp GR, Parks MM. Filtering surgery in children: barriers to success. *Ophthalmology* 1979;**86**:170–80.
38 Miller MH, Rice NSC. Trabeculectomy combined with β irradiation for congenital glaucoma. *Br J Ophthalmol* 1991; **75**:584–90.
39 Gressel MG, Heuer DK, Parrish RK II. Trabeculectomy in young patients. *Ophthalmology* 1984;**91**:1242–6.
40 Jerndal T, Lundstrom M. 330 trabeculectomies: a long-time study: 3–5½ years. *Acta Ophthalmol* 1980:**58**:947–56.
41 Cairns JE. Trabeculectomy—preliminary report. *Am J Ophthalmol* 1968;**66**:673.
42 Watson PG. Trabeculectomy: a modified ab externo technique. *Ann Ophthalmol* 1970;**2**:1918.
43 Chen CW. Enhanced intraocular pressure controlling effectiveness of trabeculectomy by local application of mitomycin C. *Trans Asia-Pacific Acad Ophthalmol* 1983;**9**:172–7.
44 Chen CW, Huang HT, Bair JS, *et al*. Trabeculectomy with simultaneous application of mitomycin C in refractory glaucoma. *J Ocul Pharm* 1990;**6**:175–82.
45 Palmer SS. Mitomycin as adjunct chemotherapy with trabeculectomy. *Ophthalmology* 1991;**98**:317–21.
46 Ramakrishnan R, Michon J, Robin AL, *et al*. Safety and efficacy of mitomycin C trabeculectomy in southern India. A short-term pilot study. *Ophthalmology* 1993;**100**:1619–23.
47 Lamping KA, Belkin JK. 5-Fluorouracil and mitomycin C in pseudophakic patients. *Ophthalmology* 1995;**102**:70–5.
48 Joos KM, Bueche MJ, Palmberg PF, *et al*. One-year follow-up results of combined mitomycin C trabeculectomy and extracapsular cataract extraction. *Ophthalmology* 1995;**102**:76–83.
49 Singh J, O'Brien C, Chawla HB. Success rate and complications of intraoperative 0.2mg/ml mitomycin C in trabeculectomy surgery. *Eye* 1995;**9**:460–6.
50 Tressler CS, Cyrlin MN, Rosensheim JS, *et al*. Subconjunctival versus intrascleral mitomycin-C in trabeculectomy. *Ophthalmol Surg Lasers* 1996; **27**:661–6.
51 Megavand GS, Salmon JF, Scholtz RP, *et al*. The effect of reducing the exposure time of mitomycin C in glaucoma filtering surgery. *Ophthalmol*ogy 1995;**102**:84–90.
52 Prata JA, Minckler DS, Baerveldt G, *et al*. Trabeculectomy in pseudophakic patients: postoperative 5 fluorouracil versus intraoperative mitomycin C antiproliferative therapy. *Ophthalmic Surg* 1995;**26**:73–7.
53 Skuta GL, Beeson CB, Higginbotham AJ, *et al*. Intraoperative mitomycin versus postoperative 5-fluorouracil in high-risk glaucoma filtering surgery. *Ophthalmology* 1992;**99**: 438–44.
54 Zacharia PT, Deppermann SR, Schuman JS. Ocular hypotony after trabeculectomy with mitomycin C. *Am J Ophthalmol* 1993;**116**:314–26.
55 Seah SKL, Prata JA Jr, Minckler DS, *et al*. Mitomycin C concentration in human aqueous humour following trabeculectomy. *Eye* 1993;**7**:625–55.
56 Kawase K, Matsushita H, Yamamoto T, *et al*. Mitomycin C concentration in rabbit and human ocular tissues after topical administration. *Ophthalmology* 1992;**99**:203–7.
57 Kawase K, Nishimura K, Yamamoto T, *et al*. Anterior chamber reaction after mitomycin and 5-fluoruoracil trabeculectomy: a comparative study. *Ophthalmic Surg* 1993;**24**:24–7.
58 Ophir A, Ticho U. Encapsulated filtering bleb and subconjunctival 5-fluoruoracil. *Ophthalmic Surg* 1995;**26**:57–60.
59 Campagna JA, Munden PM, Alward WLM. Tenon's cyst formation after trabeculectomy with mitomycin C. *Ophthalmic Surg* 1995;**26**:57–60.
60 Katz LJ, Cantor LB, Spaeth GL. Early and late bacterial endophthalmitis following glaucoma filtering surgery. *Ophthalmology* 1985;**92**:959–63.
61 Hattenhauer JM, Lipisch MP. Late endophthalmitis after filtering surgery. *Am J Ophthalmol* 1971;**72**:1097–101.
62 Costa VP, Spaeth GL, Eiferman RA, *et al*. Wound healing modulation in glaucoma filtration surgery. *Ophthalmic Surg* 1993;**24**:152–70.
63 Jampel HC. Effect of brief exposure to mitomycin C on viability and proliferation of cultured human Tenon's fibroblasts. *Ophthalmology* 1992;**99**:1471–6.
64 Bergstrom TJ, Wilkinson WS, Skuta GL, *et al*. The effects of subconjunctival mitomycin C on glaucoma filtration surgery in rabbits. *Arch Ophthalmol* 1991;**109**:1725–30.
65 Shields MB, Scroggs MW, Sloop CM, *et al*. Clinical and histopathological observations concerning hypotonyy after trabeculectomy with adjunctive mitomycin C. *Am J Ophthalmol* 1993;**116**:673–83.
66 Rubinfield RS, Pfister RR, Stein RM, *et al*. Serious complications of topical mitomycin C after pterygium surgery. *Ophthalmology* 1992;**99**:1647–54.
67 Smith S, D'Amore PA, Dreyer EB. Comparative toxicity of mitomycin C and 5-fluoruoracil in vitro. *Am J Ophthalmol* 1994;**118**:332–7.
68 Chi HH, Teng CC, Katzin HM. Experimental implants of sclera into the anterior chamber. *Am J Ophthalmol* 1959;**46**:534–41.
69 Herschler J, Claflin AJ, Fiorentino G. The effect of aqueous humor on the growth of subconjunctival fibroblasts in tissue culture and its implications for glaucoma surgery. *Am J Ophthalmol* 1980;**89**:245–9.
70 Herscher J. The inhibitory factor in aqueous humour. *Vis Res* 1981;**21**:163.
71 Okumura S, Deguchi T, Nakamizo N. Studies on the physiological deposition and pharmacokinetics of 7-N-(p-hydroxyphenyl)-mitomycin C. *Jpn J Antibiot* 1982;**35**: 1967–76.