Long term results and complications of trabeculectomy augmented with low dose mitomycin C in patients at risk for filtration failure

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Abstract

***Aim*—To determine the results and complications up to 5 years after trabeculectomy with 0.02% mitomycin C (MMC) in glaucoma patients at risk for failure of filtration surgery.**

***Methods*—A consecutive series of 21 eyes from 20 patients who underwent trabeculectomy with MMC 0.02%, with an exposure time of 2 minutes, was retrospectively analysed and the results were compared with previously published data.**

***Results*—The mean preoperative intraocular pressure (IOP) was 28 mm Hg on an average of 2.8 glaucoma medications, and the mean postoperative IOP after 3 years was 14 mm Hg on an average of 0.4 medications. Three years after trabeculectomy, 17 of 21 (80.9%) eyes had an IOP of less than 21 mm Hg without medical treatment. Using Kaplan-Meier life table analysis the 5 year probability of an IOP less than 21 mm Hg without medication was 67% and with medication was 90%. Two patients required further glaucoma surgery during the first postoperative year, and another developed hypotonous maculopathy which was reversed after bleb revision. Seven patients developed visually significant cataract as a late consequence of the surgery. There were no bleb related infections.**

***Conclusion*—In the long term MMC 0.02% used for 2 minutes intraoperatively is an effective adjunctive treatment in glaucoma patients at risk for bleb failure and in this dose is associated with few complications.**

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Mitomycin C (MMC) has revolutionised the treatment of glaucoma patients at high risk for failure of filtration surgery and although the short and intermediate term success rates of trabeculectomy with MMC have been well described,[1–16] there is a paucity of long term follow up data in the literature on the effects of MMC.[17 18] In addition, despite the widespread use of MMC, there is still debate about the optimal concentration, exposure time, and delivery vehicle for this drug. In the absence of definitive data, glaucoma surgeons use a wide range of concentrations and exposure times.[19] The use of MMC at a low dose holds the promise of a reduced complication rate, but at the possible expense of a reduced success rate in patients at risk for failure. Some investigators have reported short term data regarding the efficacy and complication rate of trabeculectomy augmented with 0.02% MMC,[5–14] but long term follow up data have not been published.

We analysed the results and complications of a consecutive series of patients undergoing trabeculectomy augmented with 0.02% MMC for 2 minutes and compared these results with published data. The duration of follow up of our series of patients is one of the longest yet reported after trabeculectomy with MMC.

Methods

We reviewed the operations which were performed by one surgeon (JFS) at the Oxford Eye Hospital during the period July 1994 to April 1997 and identified 21 eyes of 20 consecutive patients at risk for bleb failure who had undergone a trabeculectomy with MMC. We studied the clinical records of these patients with particular attention to the aetiology of the glaucoma, the preoperative and postoperative intraocular pressure (IOP) at each follow up, the bleb appearance, the need for postoperative medical glaucoma treatment, the need for re-operation, the complications of surgery, and the change in vision. No patients were lost to follow up and all patients were followed for at least 3 years postoperatively.

In all cases the surgery was performed using a superior rectus bridle suture and a fornix based conjunctival flap. After haemostasis was obtained, MMC was applied between the sclera and Tenon's capsule for 2 minutes with a surgical sponge measuring 4.5 mm × 4.5 mm which had been soaked in a 0.2 mg/ml solution. After 2 minutes the sponge was removed and the entire surgical field was irrigated thoroughly with balanced saline solution. A 4 mm × 4 mm scleral flap was fashioned 1 mm into clear cornea, a 1 mm × 2 mm scleral block was excised, and a peripheral iridectomy was created. The scleral flap was closed with four interrupted 10-0 nylon sutures and the conjunctiva was closed tightly with interrupted 10-0 nylon sutures. A subconjunctival injection of 20 mg gentamicin and 2.0 mg betamethasone was administered in the inferior fornix. Postoperatively all patients received dexamethasone 0.1%/neomycin four times daily for 2 weeks and homatropine 1% twice daily for 1 week. At 2 weeks the antibiotic was stopped and prednisolone acetate 1% was used four

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times daily for a further 1–2 months. In no patient was postoperative manipulation of the bleb required.

To compare our results with others, surgery was defined as a "complete success" when the IOP was less than 21 mm Hg without glaucoma medication, a "qualified success" when the IOP was less than 21 mm Hg with or without glaucoma medication, and a "failure" when the IOP was greater than or equal to 21 mm Hg with medical treatment or when repeat surgery was required. Hypotony was defined as an IOP less than 5 mm Hg, documented at two postoperative visits separated by at least 1 week. The cumulative survival of the eyes considered a success was determined using Kaplan-Meier life table analysis.

Results

There were 11 male and nine female patients in the study with an average age of 65 years and an average follow up of 53.3 months (range 36–69 months). One male patient and two female patients were black and the remainder were white. Fifteen patients were followed for at least 4 years and 10 patients were followed for at least 5 years. The risk factors for bleb failure are shown in Table 1. Eight patients had two risk factors for failure and there were no patients with neovascular glaucoma. All previous cataract surgery had been performed using a corneal incision. Four patients had chronic anterior uveitis, but no intraocular inflammation was present at the time of surgery. In the early postoperative period there were two cases of a transient early hyphaema and no cases of a shallow or flat anterior chamber occurred. There were no late bleb related infections.

The average preoperative IOP was 28 mm Hg (range 22–45 mm Hg) on an average of 2.8 medications, and the mean postoperative IOP after 3 years was 14 mm Hg (range 10–26 mm Hg) on an average of 0.4 medications. After 3 years, 17 eyes (81%) were classified as a complete success. Two patients required medical treatment during this period, therefore 90.5% (19/21) had an IOP less than 21 mm Hg with or without medication and were classified as a qualified success. Of these patients, 78.9% (15/19) had an IOP less than 16 mm Hg at the last postoperative visit. Two further patients required medical treatment during the fourth postoperative year in order to maintain their target pressures of 18 mm Hg. The cumulative survival of the complete and qualified successes by Kaplan-Meier life table analysis is shown in Figure 1. At 5 years, the probability of success allowing for the different lengths of follow up was 67%; similarly there was a 90%

Table 1 Risk factor for bleb failure

Risk factor for failure	*Number*
Previous failed trabeculectomy	7
Previous failed trabeculectomy and Afro-Caribbean race	2
Previous failed trabeculectomy and cataract extraction	4
Previous cataract extraction	2
Previous cataract extraction and Afro-Caribbean race	1
Uveitis	3
Uveitis and age less than 50	1
Age less than 50	1

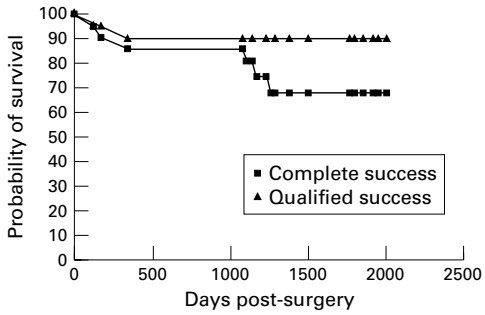

Figure 1 Surgical cumulative success rates by Kaplan-Meier life table analysis. "Complete success" is defined as an IOP less than 21 mm Hg without medication. "Qualified success" is defined as an IOP less than 21 mm Hg with or without medication.

probability of qualified success. Only two eyes were classified as a failure, and required further surgery within 1 year of the initial trabeculectomy. In both cases the IOP was subsequently successfully controlled. Of the 17 patients classified as a complete success, 10 (58.8%) had a cystic bleb, five (29.4%) had a diffuse microcystic bleb, and two (11.8%) had a shallow bleb. The four patients using glaucoma medication had either a shallow or absent bleb.

Six patients had lost two or more lines of Snellen acuity at the last follow up visit compared with their preoperative acuity. In four cases visual deterioration was due to cataract and in two the visual deterioration was due to progression of glaucoma despite an IOP that was maintained below 18 mm Hg. Three further cases of visually significant cataract had occurred when these results were collated, but these patients had already undergone cataract extraction with intraocular lens implantation with significant visual improvement compared with their pre-trabeculectomy level.

There was one case of hypotony which occurred secondary to an aqueous leak at the limbus of a 45 year old man with chronic anterior uveitis. He developed hypotonous maculopathy and underwent a bleb revision 4 months after trabeculectomy which restored the IOP to 12 mm Hg and the final Snellen acuity to 6/6.

Discussion

It is well established that the intraoperative application of MMC improves the success rate of filtering surgery in patients with risk factors for failure, at the cost of an increased complication rate.[1–21] Persistent hypotony and endophthalmitis are particularly debilitating sequelae.[3–22] Although we had no cases of bleb related infection, a lifetime risk of this complication remains, especially for those patients with cystic blebs.

Other investigators using higher concentrations or exposure times than those reported here, have found that 70–82% of high risk patients have an IOP less than 21 mm Hg with or without glaucoma medication 3 years after surgery.[1–9]

A recent survey of antimetabolite use among American and Japanese glaucoma specialists found a very wide range in exposure times (5 seconds to 7 minutes) and concentrations

(0.01%–0.08%) of MMC used in similar situations.[19] Analysis of the literature on the subject suggests that the success rate is not greatly affected by a low concentration and short exposure time of MMC, but that the complication rate rises considerably when these two variables are increased.[1–21]

Wilkins *et al* have recently shown that the dose of 5-fluorouracil to conjunctiva and sclera after sponge application to porcine eyes exhibits a saturation effect and is not enhanced beyond a 2–3 minute exposure.[23] Jampel found that 0.02% MMC applied for 1 minute inhibited fibroblasts in vitro by 68% and that the inhibition increased to 90% when 0.04% MMC was used for 5 minutes.[24] Megevand *et al* conducted a retrospective comparative study on patients at high risk for failure which supports this laboratory based evidence.[5] At 18 months the surgical success rate in a group of patients receiving 0.02% MMC for 2 minutes was similar to that found in a matched group receiving 0.02% MMC for 5 minutes.

Despite these data, there is some evidence in the literature to suggest that tissue response mechanisms may play a part in determining the risk of hypotony, independent of MMC concentration and exposure times.[6–21] Stone *et al* and Shields *et al*, in two separate studies, titrated the exposure times of MMC to the number of risk factors for failure and reported similar surgical success rates in the different exposure time subgroups.[6–21] They noted that all cases of hypotony related maculopathy occurred in those patients with the lowest risk for failure and although we have argued that a low concentration and exposure time is preferable, their finding suggests that patient variables may also be important in determining the risk of hypotony. The relative risk that can be attributed to each factor and the manner in which multiple risk factors interact in an individual remain poorly understood. In addition, it is uncertain whether risk factors in individuals are cumulative. Unfortunately, the small number of "failures" in our study meant that this issue could not be resolved. Further study into the patient variables that determine the fibrotic response and the susceptibility to complications such as hypotonous maculopathy would greatly enhance our ability to treat these challenging patients.

We have shown that 0.02% MMC applied for 2 minutes between the sclera and Tenon's capsule of patients at risk for failure is at least as effective as that reported in the literature using higher doses and exposure times, and in this dose is associated with few serious complications. This study has also demonstrated the long term efficacy and safety of low dose MMC. Limitations of our study include its retrospective nature and the relatively small number of patients involved. Given the widespread use of intraoperative 5-fluorouracil in the United Kingdom, it would be interesting to compare 0.02% MMC with 5-fluorouracil in patients at risk for failure of trabeculectomy, by means of a randomised trial.

1 Perkins TW, Gangnon R, Ladd W, *et al*. Trabeculectomy with mitomycin C: intermediate-term results. *J Glaucoma* 1998;**7**:230–6.
2 Cheung JC, Wright MM, Murali S, *et al*. Intermediate-term outcome of variable dose mitomycin C filtering surgery. *Ophthalmology* 1997;**104**:143–9.
3 Costa VP, Moster MR, Wilson RP. Effects of topical mitomycin C on primary trabeculectomies and combined procedures. *Br J Ophthalmol* 1993;**77**:693–7.
4 Lamping K, Belkin J. 5-Fluorouracil and mitomycin C in pseudophakic patients. *Ophthalmology* 1995;**102**:70–5.
5 Megevand GS, Salmon JF, Scholtz RP, *et al*. The effect of reducing the exposure time of mitomycin C in glaucoma filtering surgery. *Ophthalmology* 1995;**102**:84–90.
6 Stone RT, Herndon LW, Allingham RR, *et al*. Results of trabeculectomy with 0.3 mg/ml mitomycin C titrating exposure times based on risk factors for failure. *J Glaucoma* 1998;**7**:39–44.
7 Palmer SS. Mitomycin as adjunct chemotherapy with trabeculectomy. *Ophthalmology* 1991;**98**:317–21.
8 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.
9 Kitazawa Y, Kawase K, Matsushita H, *et al*. Trabeculectomy with mitomycin: a comparative study with fluorouracil. *Arch Ophthalmol* 1991;**109**:1693–8.
10 Chen C-W, Huang H-T, Bair J-S, *et al*. Trabeculectomy with simultaneous topical application of mitomycin C in refractory glaucoma. *J Ocul Pharmacol* 1990;**6**:175–82.
11 Mietz H, Krieglstein GK. Short-term clinical results and complications of trabeculectomies performed with mitomycin C using different concentrations. *Int Ophthalmol* 1995;**19**:51–6.
12 Beatty S, Potamitis T, Kherterpal S, *et al*. Trabeculectomy augmented with MMC application under the scleral flap. *Br J Ophthalmol* 1998;**82**:397–403.
13 Singh C, O'Brien C, Chawla HB. Success rates and complications of intraoperative 0.2mg/ml mitomycinC in trabeculectomy surgery. *Eye* 1995;**9**:460–6.
14 Smith MF, Doyle JW, Nguyen QH, *et al*. Results of intraoperative 5-fluorouracil or lower dose mitomycin C administration on initial trabeculectomy surgery. *J Glaucoma* 1997;**6**:104–10.
15 Katz GJ, Higginbotham EJ, Lichter PR, *et al*. Mitomycin C versus 5-fluorouracil in high-risk glaucoma filtering surgery. *Ophthalmology* 1995;**102**:1263–9.
16 Prata JA, Seah SKL, Minckler DS, *et al*. Postoperative complications and short-term outcome after 5-fluorouracil or mitomycin C trabeculectomy. *J Glaucoma* 1995;**4**:25–31.
17 Hagiwara Y, Yamamoto T, Kitazawa Y. The effect of mitomycin C trabeculectomy on the progression of visual field defect in normal-tension glaucoma. *Graefes Arch Clin Exp Ophthalmol* 2000;**238**:232–6.
18 Jacobi PC, Dietlein TS, Krieglstein GK. Adjunctive mitomycin C in primary trabeculectomy in young adults: a long-term study of case matched young patients. *Graefes Arch Clin Exp Ophthalmol* 1998;**236**:652–7.
19 Chen PP, Yamamoto T, Sawada A, *et al*. Use of antifibrosis agents and glaucoma drainage devices in the American and Japanese Glaucoma Societies. *J Glaucoma* 1997;**6**:192–196.
20 Zacharia PT, Depperman SR, Schuman JS. Ocular hypotony after trabeculectomy with MMC. *Am J Ophthalmol* 1993;**116**:314–26.
21 Shields MB, Scroggs MW, Sloop CM, *et al*. Clinical and histopathologic observations concerning hypotony after trabeculectomy with adjunctive mitomycin C. *Am J Ophthalmol* 1993;**116**:673–83.
22 Greenfield DS, Suner IJ, Miller MP, *et al*. Endophthalmitis after filtering surgery with mitomycin. *Arch Ophthalmol* 1996;**114**:943–9.
23 Wilkins MR, Occleston NL, Kotecha A, *et al*. Sponge delivery variables and tissue levels of 5-fluorouracil. *Br J Ophthalmol* 2000;**84**:92–97.
24 Jampel HD. Effect of brief exposure to mitomycin C on viability and proliferation of cultured human Tenon's capsule fibroblasts. *Ophthalmology* 1992;**99**:1471–6.