Success rate and complications of intraoperative 0.2 mg/ml Mitomycin C in trabeculectomy surgery

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SUCCESS RATE AND COMPLICATIONS OF INTRAOPERATIVE 0.2 mg/ml MITOMYCIN C IN TRABECULECTOMY SURGERY

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SUMMARY

Adjunctive chemotherapy with Mitomycin C (MMC) has been used in an attempt to modulate the wound healing response in glaucoma filtration surgery. A consecutive series of 20 eyes from 18 patients undergoing trabeculectomy with MMC intraoperatively was studied. Sixteen cases were considered high risk regarding surgical success and 4 patients with low tension glaucoma (LTG) required lower intraocular pressure (IOP) to prevent further visual field loss. Surgical technique involved the use of a limbal-based conjunctival flap and MMC 0.2 mg/ml applied via a sponge (under the scleral flap) to both scleral and conjunctival surfaces for 5 minutes. The mean follow-up period was 12.7 months (range 3–24). There were 17 successful eyes. Of these, 14 are high pressure glaucoma eyes with a mean pre-operative IOP of 30.9 ± 10.9 mmHg and a mean postoperative IOP of 15.3 ± 5.2 mmHg ($p = 0.001$). The remainder of the successful cases include 4 patients with LTG with a mean pre-operative IOP of 17.8 ± 0.5 mmHg and a mean post-operative IOP of 6.8 ± 0.7 mmHg ($p = 0.001$). Serious complications included chronic repeated bleb leaks ($n = 2$) and scleral necrosis ($n = 2$). There was one case of hypotonous maculopathy. These results are comparable with those of other studies. Despite a relatively low dose of MMC serious side-effects were encountered. Management of these complications is described, and how these effects may be prevented by altering scleral exposure to MMC. In addition a possible explanation for the serious side-effects of MMC-treated trabeculectomies is presented.

Failure of glaucoma filtration surgery can be attributed to excessive healing under the Tenon's/conjunctival lamina. The major cellular component responsible for this reaction is thought to be fibroblasts derived from local tissues.[1,2] Although this pathological process is a normal response to surgical trauma it may be modulated with adjunctive chemotherapy.

Mitomycin C (MMC) was first used in ophthalmology post-operatively in a topical form after pterygium surgery to prevent recurrence of this condition.[3] This drug is an antibiotic originally isolated in Japan in 1954 from the broth of a fungus *Streptomyces caespitosus* and has anti-tumour activity due to its alkylating effects preventing DNA synthesis.[4] MMC has also been shown to inhibit Tenon's capsule/conjunctival fibroblast proliferation *in vitro* using cell culture techniques.[5–8] This latter effect of MMC has been applied *in vivo* to modify the healing response after glaucoma filtration surgery in eyes regarded as high-risk cases, such as eyes that have undergone previous failed glaucoma surgery, aphakic eyes, black or Asian eyes and eyes of patients requiring very low intraocular pressure.[9–16] These studies have used a wide variation in the concentration and exposure duration of MMC employed for filtration surgery. This series addresses the surgical success rate and complications of trabeculectomy using 0.2 mg/ml MMC.

PATIENTS AND METHODS

We looked at a consecutive series of 20 eyes from 18 patients that have undergone glaucoma filtration surgery using MMC as an adjunct. The mean follow-up period was 12.7 months (range 3–24 months). There were 7 men and 11 women and all are Caucasian. The average age was 64.5 years (range 36–92 years). Sixteen patients in this study were considered as high risk regarding successful glaucoma filtration surgery and 4 patients with low tension glaucoma (LTG) required low intraocular pressure (IOP) to prevent further visual field loss.

All patients underwent a complete ocular examination before and after surgery including best corrected visual acuity, IOP measurement by

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Goldmann applanation tonometry, optic disc assessment by indirect ophthalmoscopy using either the +90 dioptre or +78 dioptre Volk lens, and visual field assessment if the acuity permitted. Surgical technique involved the use of a limbal-based conjunctival flap, bipolar cautery to the sclera and a half-thickness rectangular scleral flap 4 mm × 4 mm created to clear cornea. A surgical sponge (Sugi Steril, John Weiss & Son Ltd) measuring 4 mm × 3 mm was soaked in a solution of 0.2 mg/ml MMC (Mitomycin C Kyowa powder was reconstituted in sterile water to give the final concentration). This sponge was placed under the dissected scleral flap and the conjunctival flap was also draped over the MMC-soaked sponge so that only those ocular tissues in contact with the sponge were directly exposed to MMC. The sclera and the Tenon's/conjunctival surfaces were exposed to MMC for exactly 5 minutes. After this time the MMC was irrigated thoroughly with 20 ml balanced salt solution. A block of corneoscleral tissue was excised and a peripheral iridectomy performed. The scleral flap was sutured with either 10/0 nylon or 8/0 virgin silk and the conjunctiva closed with either 10/0 nylon or 8/0 virgin silk. Post-operative medications included betamethasone 0.1% with neomycin four times a day and cyclopentolate 1% twice daily. Visual acuity and intraocular measurements were made post-operatively at 1 day, 1 week, 1 month, 3 months and at the latest follow-up or between these times if the clinical situation demanded. All complications were recorded.

A complete surgical success is defined as an intraocular pressure of 21 mmHg or less without any anti-glaucoma treatment. A qualified success is defined as an intraocular pressure of 21 mmHg or

Table I. Essential clinical details

Case	Age (years)	Eye	Diagnosis	Previous surgery in same eye	Acuity		Medications		IOP (mmHg)		Success	Follow-up (months)
					Pre-op.	Post-op.	Pre-op.	Post-op.	Pre-op.	Post-op.		
1	76	R	POAG	Trabeculectomy	6/12	6/12	Betaxolol	Betaxolol	26	20	Qualified	17
2	51	R	POAG	Two trabeculectomies followed by Molteno valve	6/5	6/4	Timolol	Nil	36	13	Complete	19
3	56	R	POAG	Trabeculectomy	6/5	6/5	Betaxolol/ pilocarpine	Nil	42	8	Complete	8
4	56	L	POAG	Trabeculectomy	6/5	6/9	Betaxolol/ pilocarpine	Nil	26	10	Complete	8
5	74	L	POAG	Trabeculectomy	6/6	6/12	Timolol/ pilocarpine/ propine	Nil	32	9	Complete	12
6	76	L	POAG	Trabeculectomy	6/9	6/9	Timolol/ pilocarpine	Timolol	24	19	Qualified	24
7	63	R	POAG	Trabeculectomy	6/9	6/9	Timolol/ pilocarpine	Nil	25	12	Complete	19
8	63	L	POAG	Trabeculectomy	6/6	6/9	Timolol/ pilocarpine	Nil	26	19	Complete	13
9	51	L	POAG	Trabeculectomy	6/12	6/12	Timolol	Nil	26	16	Complete	12
10	82	L	LTG	None	6/6	6/9	Timolol/ propine	Nil	18	6	Complete	18
11	66	L	LTG	None	6/9	6/18	Carteolol	Nil	18	9	Complete	12
12	74	R	LTG	None	6/9	6/9	Timolol/ propine	Nil	18	7	Complete	11
13	79	L	LTG	None	6/36	6/36	Timolol/ pilocarpine	Nil	17	5	Complete	3
14	62	R	CACG	YAG PI, trabeculectomy	6/6	6/9	Timolol/ diamox	Timolol	24	25	Failure	12
15	45	R	Fuchs' heterochromic cyclitis	ECCE, secondary IOL	6/9	6/9	Timolol/ diamox	Nil	32	12	Complete	12
16	36	L	Pigmentary glaucoma	Trabeculectomy	6/6	6/9	Timolol	Nil	26	19	Complete	6
17	91	R	Pupil block glaucoma	ECCE and IOL trabeculectomy	PL	PL	Timolol/ diamox	Nil	64	11	Complete	12
18	45	L	Panuveitis	Trabeculectomy	6/9	6/9	Timolol/ propine	Timolol	24	21	Qualified	4
19	58	L	Penetrating injury, vitreous haemorrhage	Corneal repair, vitrectomy, trabeculectomy	PL	PL	Timolol	Timolol	36	34	Failure	22
20	92	R	CACG	YAG PI, trabeculectomy	HM	HM	Timolol/ propine	Timolol	26	30	Failure	4

R, right; L, left; POAG, primary open angle glaucoma; CACG, chronic angle closure glaucoma; LTG, low tension glaucoma; PI, peripheral iridotomy; ECCE and IOL, extracapsular cataract extraction and lens implant; PL, perception of light; HM, hand movements; IOP, intraocular pressure.

Table II. Pre-operative and post-operative IOPs in the patients with high pressure glaucoma and low tension glaucoma

	Mean pre-operative IOP (mmHg)	Mean post-operative IOP (mmHg)	Student's *t*-test
High pressure glaucoma (n = 14)	30.9 range 24–42 (± 10.9)	15.3 range 8–20 (± 5.2)	$p = 0.001$
Low tension glaucoma (n = 4)	17.8 range 17–18 (± 0.5)	6.8 range 5–7 (± 0.7)	$p = 0.001$

less with anti-glaucoma treatment. A failure is defined as an intraocular pressure of greater than 21 mmHg regardless of any medication.

RESULTS

The essential details of all the cases are presented in Table I.

There were 9 patients with primary open angle glaucoma, 2 with chronic angle closure glaucoma, 1 with pigmentary glaucoma, 1 with panuveitis and secondary glaucoma, and 1 with pupil block glaucoma. All these patients had undergone at least one previous failed filtration procedure and were thus considered to be high risk regarding surgical success. One patient with Fuchs' heterochromic cyclitis and secondary glaucoma had undergone two previous intraocular procedures and was also included in the high-risk category being aphakic. In addition 4 patients with low tension glaucoma underwent trabeculectomy with MMC as a primary procedure. The mean follow-up period was 12.7 months with a range of 3–24 months. Fourteen eyes were followed up for 12 months or more.

The overall success is 85% (17 eyes), i.e. an IOP of 21 mmHg with or without additional anti-glaucoma medication. Complete success occurred in 70% (14 eyes) of cases, i.e. an IOP of 21 mmHg or less without any further anti-glaucoma treatment. The mean pre-operative IOP for the 16 high pressure glaucoma patients was 30.9 range 24–42 (± 10.9) mmHg with a final post-operative IOP of 15.3 range 8–20 (± 5.2) mmHg. Also the 4 patients with LTG had a mean pre-operative IOP of 17.8 range 17–18 (± 0.5) mmHg and a final post-operative IOP of 6.8 range 5–7 (± 0.7) mmHg without any medication. These results are statistically significant as outlined in Table II. Failure, defined as an intraocular pressure of >21 mmHg, was 15% (3 eyes) in this study.

Complications did arise and are summarised in Table III. Two complications occurred in patient 10 who developed a bleb leak 1 month post-operatively and a diffuse superficial punctate keratitis. The leak sealed off spontaneously over 2 days and the keratitis also settled with no significant effect on visual acuity and is categorised by definition a complete success. Only 1 patient developed cataract, accounting for a change in vision from 6/6 to 6/12.

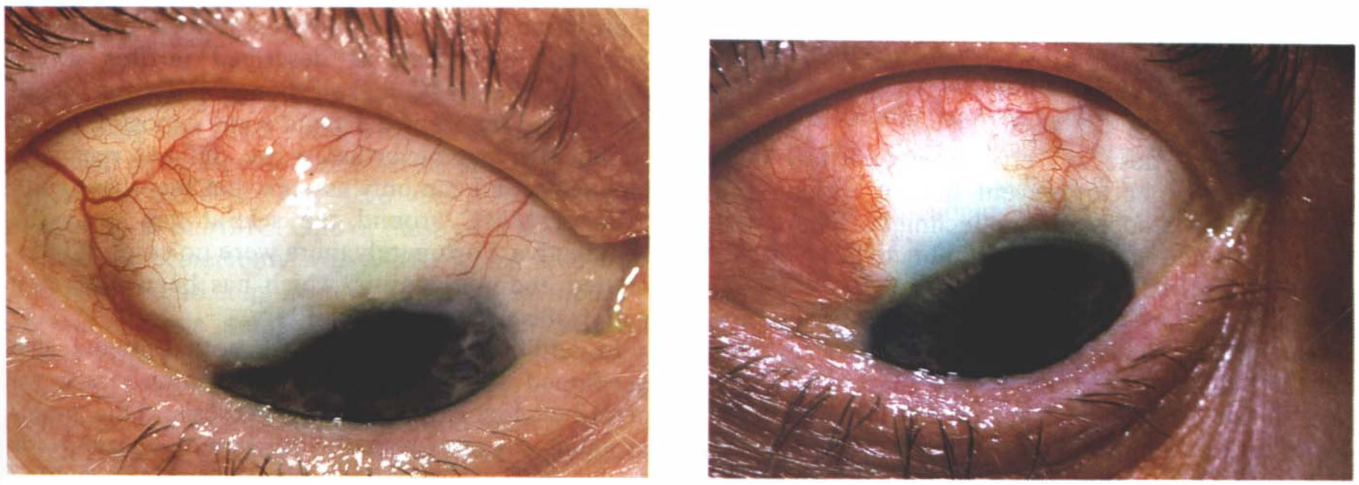
Table III. Complications

Type of complication	No.	%
Scleral necrosis	2	10
Recurrent bleb leak	2	10
Shallow anterior chamber	2	10
Hypotonous maculopathy	1	5
Cataract progression	1	5
Single bleb leak	1	5
Corneal toxicity (punctate staining)	1	5
Late bleb endophthalmitis	0	0

Serious problems were also encountered in patients 8 and 11. In the former case there were repeated bleb leaks. The first occurred 10 months post-operatively and was treated with cyanoacrylate glue, but this procedure needed to be repeated 2 days later. Another leak occurred 10 days later at a different site on the bleb and the conjunctiva was surgically refashioned. However, the leak persisted and the trabeculectomy site was explored surgically, when it was found that in addition to the conjunctival leak there was also an area measuring approximately 3 mm × 3 mm adjacent to the original scleral flap door which was completely avascular, very thin and friable, exposing the underlying ciliary body. Clinically this area appeared similar to scleral necrosis or scleral melting and was leaking aqueous by Siedal testing with fluorescein. The defect was repaired by creating a partial-thickness scleral flap adjacent to the area of aqueous leakage, this flap of sclera being overturned to cover the necrotic area and sutured into place with 10/0 nylon, the conjunctiva being repaired again using 8/0 vicryl. Unfortunately the conjunctiva broke down again and another leak at a different site on the bleb developed 10 days later. This was treated with cyanoacrylate glue and a large bandage contact lens. The eye eventually settled 12 months post-operatively with a final IOP of 19 mmHg without any glaucoma medication and an acuity of 6/9 (Figs. 1, 2b).

The second serious complication affected patient 11. Again the major problem began with a bleb leak 4 days after filtration surgery. The IOP was 2 mmHg and the conjunctiva was refashioned. The IOP improved to 6 mmHg but the patient complained of deteriorating vision 3 months post-operatively and was found to have a hypotonous maculopathy. This was confirmed on fluorescein angiography (Fig. 3). Another bleb leak developed at a different site from the original one with an unrecordable IOP 10 months post-operatively and the conjunctiva was surgically repaired again. The IOP did not improve but a larger bleb leak occurred. The trabeculectomy site was explored surgically and it was found that this patient also had an area clinically resembling scleral necrosis with aqueous leakage adjacent to the original flap door. This defect was again completely avascular, extremely thin and friable, exposing the ciliary body;

Fig. 1. *This patient (cases 3 and 4) has had bilateral MMC trabeculectomies. The photograph shows the typical appearance of blebs treated with MMC. Both eyes have had previous trabeculectomies which failed.*



(a) (b)

Fig. 2. *Both photographs are higher magnifications of Fig. 1 showing more detail. The right eye was uncomplicated. The left eye suffered repeated bleb leaks and scleral necrosis and took over 12 months to settle. Note the profound avascular nature of the blebs. MMC has been shown* in vitro *to be cytotoxic to both fibroblasts and capillary endothelial cells.*[31]

it measured approximately 3 mm × 3 mm. This area was repaired in a similar way to the case above and the conjunctiva refashioned yet again. Unfortunately another bleb leak occurred 17 days later and this was treated with cyanoacrylate glue and a large bandage contact lens. The eye settled eventually 12.5 months after the MMC trabeculectomy. The latest IOP is 9 mmHg with no medication, but the latest visual acuity is 6/18 due to persistent macular folds.

DISCUSSION

Modulation of the wound healing process after surgical trauma in glaucoma filtration surgery has aroused widespread interest. It was Chen in 1983 who first described using MMC as an adjunct in glaucoma surgery.[9] Despite this it was 5-fluorouracil (5-FU) which gained popularity as an anti-proliferative drug in glaucoma filtration surgery and has been the drug of choice in difficult cases for some centres.[17-22] However, there are a number of problems associated with this latter chemotherapeutic agent including bleb leaks, corneal erosions, corneal melts, persistent corneal opacification, hypotonous maculopathy and the need for repeated painful subconjunctival injections.[21,22] These complications have led to the use of MMC as a possible safer alternative. This particular alkylating agent has the advantage that it may be used as a single application intraoperatively during trabeculectomy surgery, avoiding repeated injections and thus circumventing some of the complications associated with 5-FU. The anti-proliferative properties of MMC have emanated from tissue culture studies where fibroblast growth has been shown to be inhibited.[5–8] This rationale has been applied to filtration surgery; however, the dose used clinically has varied since it is difficult to extrapolate *in vitro* results to the *in vivo* situation. Thus far in the literature the dose of MMC used clinically has varied between 0.02 and 0.5 mg/ml.[10–16] We chose the 0.2 mg/ml concentration in the

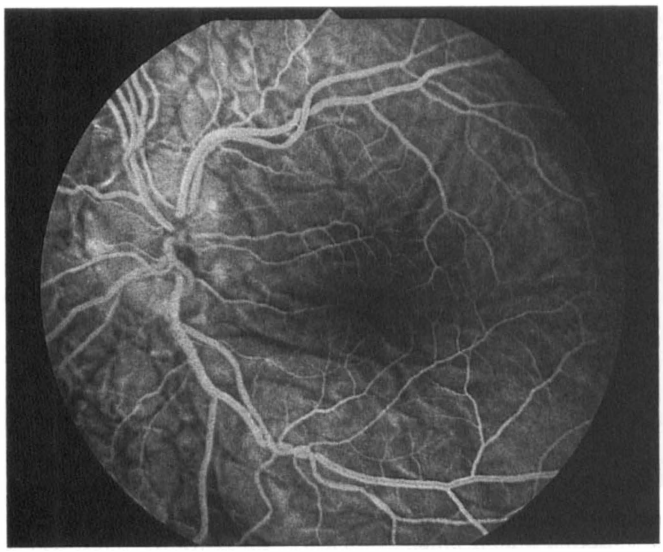


Fig. 3. *This patient's visual acuity worsened after MMC trabeculectomy due to hypotonous maculopathy. Fluorescein angiography confirmed the presence of retinal folds, which have persisted despite an improvement in the IOP to 9 mmHg.*

belief that this dose was efficacious with few side-effects.[12] In order to prevent fibrosis around the scleral flap we adopted the technique where the scleral bed and the Tenon's/conjunctival layer are exposed to MMC.[11]

While the overall results in this series are encouraging, serious complications did occur and must be taken into account. Firstly, there was only 1 case of hypotonous maculopathy (5%). This is a devastating problem and the incidence in our series is in keeping with other series.[11–14] A retrospective study[23] found ocular hypotony (IOP <5 mmHg) in 32.7% but only 2 eyes suffered from hypotonous maculopathy. This group used a concentration of 0.4 mg/ml MMC, exposure times of between 3.5 and 7 minutes, and additional sponges soaked in the same concentration of MMC that were applied to the edges of the scleral flap resulting in a greater surface area of exposure. These factors may have led to such a high incidence of ocular hypotony and may be attributed directly to MMC as it has been suggested that this compound is toxic to the ciliary body.[24] Hypotonous maculopathy is an unacceptable risk and this complication may occur more readily when using MMC.

Repeated bleb leaks were a frustrating problem in 2 patients. These were chronic complications lasting approximately 12 months in both cases, with one patient described above developing hypotonous maculopathy. Conjunctival leaks have been reported before,[13] whilst other studies have encountered no such problems with MMC.[16,17] However, there appear to be no previous reports of chronic recurrent bleb leak as described in this series. Applying the MMC-soaked sponge under the scleral flap should theoretically avoid some exposure to the conjunctiva but nevertheless we did get recurrent bleb leaks and can only assume that there was spill-over of MMC around the scleral flap onto the conjunctiva. Fortunately there were no cases of bleb-related endophthalmitis, which has been described with trabeculectomy and 5-FU.[25]

In addition to these events both patients also developed another serious complication which we describe clinically as scleral necrosis. This major problem was unexpectedly discovered at surgery for conjunctival refashioning. Scleral necrosis or melting has been described after surgical removal of pterygium and adjunctive topical MMC[26,27] but has not previously been reported with MMC used

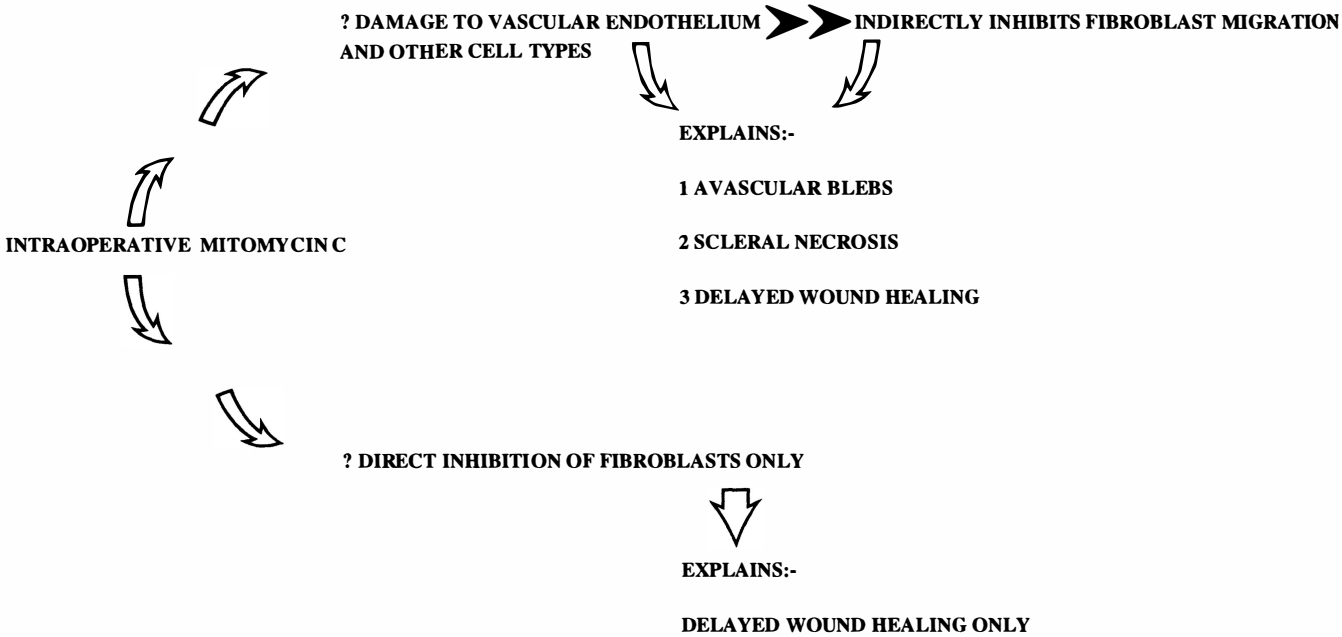


Fig. 4. *Possible mechanisms of action of Mitomycin C.*

Table IV. Bleb features following successful MMC trabeculectomy

Case no.	Bleb characteristics			
	Avascular	Cystic	Slow transconjunctival leak	Type of success
1	Yes	Yes	Yes	Qualified
2	Yes	Yes	Yes	Complete
3	Yes	Yes	Yes	Complete
4	Yes	Yes	Yes	Complete
5	Yes	Yes	Yes	Complete
7	Yes	Yes	Yes	Complete
8	Yes	Yes	Yes	Complete
9	Yes	Yes	Yes	Complete
10	Yes	Yes	Yes	Complete
11	Yes	Yes	Yes	Complete
12	Yes	Yes	Yes	Complete
13	Yes	Yes	Yes	Complete
14	No	No	No	Failure
15	Yes	Yes	Yes	Complete
16	Yes	Yes	Yes	Complete
17	Yes	Yes	Yes	Complete
18	No	No	No	Qualified

Note: case 6 was lost to follow-up and could not be reviewed for bleb characteristics.

intraoperatively for glaucoma filtration surgery. It is interesting that the 2 cases with scleral necrosis also suffered from repeated bleb leaks, and it may have been that these patients were very sensitive to the toxic effects of MMC. One of these patients (Fig. 2a) had a trabeculectomy with MMC in his fellow eye but suffered no complications. The true incidence of scleral necrosis is unknown since both cases in this study were only discovered during surgical exploration and it may well be that other patients exhibit this phenomenon with MMC in filtration surgery.

Our clinical findings with MMC and trabeculectomy surgery have led us to question the mechanism of action of this particular adjunctive agent. It is difficult to see how the experimental effects of MMC on fibroblasts alone can explain the serious problems encountered in this series. MMC is classified as an alkylating agent and is not cell-cycle-specific but has its greatest activity during DNA synthesis. The actual mechanism of interaction at the cellular level is still debated but it is thought to be activated enzymatically by cells which will bind the drug, thereafter leading to inhibition of cell division.[28,29] An alternative mechanism of action based upon the above clinical findings may be that MMC binds to other cell types including vascular endothelium[26] as well as fibroblasts. Direct damage to the vasculature (Fig. 4) may lead to avascular blebs, scleral necrosis and indirectly influence fibroblast migration; this would explain delayed wound healing since fibroblast activity can be dependent on hypoxia.[30] A recent paper has shown that MMC appears to be cytotoxic *in vitro* to fibroblasts and also to cultured capillary endothelial cells and this experimental data supports our clinical findings.[31] There are also recent studies which describe the histological appearances of blebs after trabeculectomy with MMC.[32,33] Both reports show that the conjunctiva treated with MMC has an irregular epithelium and that the underlying substantia propria is largely acellular and avascular. The work by Mietz[32] also shows that there were breaks in the basement membrane of the basal layer of the conjunctiva and suggests that these areas may facilitate aqueous drainage from the bleb. Although we are unable to provide any histological evidence to concur with this theme we would agree clinically and have found that a large proportion of the blebs in this series did show very slow leakage from the avascular conjunctiva (Table IV). We also postulate that the IOP is maintained at a low level in these particular eyes by transudation of aqueous through the conjunctiva as described previously.[34]

Many questions about MMC and its use in glaucoma filtration surgery remain unanswered. It is likely that certain complications described in this study may be avoided by using a lower dose of MMC and a reduced exposure time to the agent. Scleral necrosis may be avoided by applying MMC to the Tenon's/conjunctival layer only without prior dissection of the sclera, avoiding toxicity to an already thinned and possibly compromised area. Failure of filtration is dependent upon subconjunctival fibrosis and for this reason it would seem sensible not to apply MMC under the scleral flap. There is also evidence from animal studies that MMC applied to the scleral bed after flap dissection may cause a higher intraocular concentration of MMC compared with applying the agent directly to the sclera without prior dissection.[35] A recent paper on the use of 5-FU as a single intraoperative dose in a similar manner to MMC has shown some very good early results in filtration surgery and 5-FU may be a safer alternative to MMC.[36]

Thus it would appear beneficial to undertake a randomised multicentre trial to assess the efficacy of both 5-FU and MMC. However, we would urge more work to be done on the action of these toxic drugs on the conjunctiva to assess suitable concentrations, exposure times and the best site of application. In addition MMC has been shown to be carcinogenic and teratogenic in rodents[4] and more research needs to be directed to the toxic effect of MMC, not only to the patient but also to the operator and assistants.

Key words: Bleb leaks, Mitomycin C, Scleral necrosis, Trabeculectomy.

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