Does titration of mitomycin C as an adjunct to trabeculectomy significantly influence the intraocular pressure outcome?

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Purpose: To evaluate the benefit of titrating the concentration and exposure time of mitomycin C (MMC) as an adjunct to trabeculectomy.

Methods: This report consists of a retrospective study and a review of the literature. In the study, consecutive glaucoma patients were evaluated who underwent trabeculectomy with adjunctive MMC that was titrated for concentration and exposure time, based on patient's risk factors for surgical failure. After minimum follow-up of 6 months, patients were divided into success (intraocular pressure 7–17 mmHg), hypertension (>17 mmHg) and hypotony (<7 mmHg) groups, which were compared with regard to MMC protocol and patient variables. The literature review included reports of trabeculectomy and adjunctive MMC with and without titration.

Results: One hundred and fifty-five eyes of 155 patients were studied. There were no significant differences between the three outcome groups and MMC protocol ($p > 0.05$). The only significant patient variable was older age in the hypotony group ($p = 0.009$). The literature is conflicting regarding the value of titrating MMC as an adjunct in trabeculectomy.

Conclusion: The outcome of trabeculectomy with adjunctive MMC appears to represent a complex interaction of patient and surgical variables. While there is some support for a benefit of titrating MMC according to individual patient variables, there is inadequate evidence at the present time to claim superiority for any MMC protocol, with or without titration.

Keywords: glaucoma surgery, trabeculectomy, mitomycin C, intraocular pressure

The introduction of mitomycin C (MMC) as an adjunct to trabeculectomy was a major advance in our ability to improve the intraocular pressure (IOP) lowering efficacy of the procedure.[1–7] With it, however, came an increased risk of serious complications, including hypotony maculopathy in the early postoperative course. Many investigators have attempted to find protocols for the adjunctive therapy that will provide an acceptable balance between the benefits and risks.

The two MMC variables that have been evaluated most extensively are drug concentration and duration of application. Some surgeons have reported good results with a fixed concentration/duration protocol for all patients,[1–9] while others have attempted to improve the outcome by titrating either concentration or duration according to each patient's risk for surgical failure.[10–16] To date, there has been no compelling evidence to support the superiority of one MMC protocol over another.

The purpose of this paper is to evaluate the benefit of titrating MMC as an adjunct to trabeculectomy, based on a review of the literature and a retrospective analysis of our experience with titrating both concentration and duration of MMC in a series of patients undergoing trabeculectomy.

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Patients and methods

The medical records of a series of patients who underwent trabeculectomy with adjunctive MMC, performed at the Yale Eye Center by one surgeon (MBS), were retrospectively reviewed. The study protocol followed the guidelines of the Helsinki Declaration and was approved by the local ethics committee. For patients that underwent surgery in both eyes, one eye was randomly selected by coin toss for inclusion in the study. Concentration (0.2, 0.3, or 0.4 mg/ml) and exposure time (1–5 minutes) of MMC for each patient were determined according to a protocol based on risk factors for excessive postoperative fibrosis (Table 1). Each risk factor was assigned a score, based on past experience, the sum of which was used to determine the protocol for MMC. In some patients, the duration of MMC exposure was modified at the time of surgery based on the extent of scar tissue, bleeding, and thickness of Tenon's capsule.

Table 1 Protocol for the concentration and exposure time of mitomycin C during trabeculectomy based on risk factors for excessive postoperative fibrosis

Risk factors	Value
Age: less than 10 years	3
Age: 10–25 years	2
Age: 25–40 years	1
Age: greater than 70 years	–1
Black	1
Sturge-Weber syndrome	2
Uveitis – inactive	2
Uveitis – active	4
Neovascular glaucoma	4
Repeat filtration (1 trab/no antimetabolites)[§]	2
Repeat filtration (1 trab/5-FU)[§]	3
Repeat filtration (1 trab/MMC)[§]	4
Repeat filtration (2 or more trab)[§]	4
PCIOL[*] with virgin conjunctiva in 1 or 2 superior quadrants	1
PCIOL[*] with scar in superior quadrants	2
ACIOL[†] without vitreous in the AC[‡]	2
ACIOL[†] with vitreous in the AC[‡]	3
Aphakia	3
Other surgery with conjunctival scarring	1

Score[¶]	Concentration	Exposure time[**]
1 to 2	0.2 mg/ml	1–2 minutes
3 to 4	0.3 mg/ml	3–4 minutes
5 and over	0.4 mg/ml	5–6 minutes

Notes: [*]PCIOL, posterior chamber intraocular lens; [†]ACIOL, anterior chamber intraocular lens; [‡]AC, anterior chamber; [§]trab, trabeculectomy; [¶]Score = sum of risk factor values; [**]Actual exposure times were adjusted at the time of surgery according to bleeding, scar tissue and thickness of Tenon capsule.

A standard trabeculectomy with a limbal-based conjunctival flap was performed for all patients. A 5 × 7 mm block of polyvinyl acetal sponge, soaked in the predetermined concentration of MMC, was placed on the sclera near the limbus, prior to developing the scleral flap, and the conjunctival-Tenon capsule flap was draped over the sponge. If the duration of MMC exposure exceeded two minutes, a new sponge was used for every additional two minutes. After removing the last sponge, the exposed tissues were copiously irrigated with balanced salt solution.

Preoperative data collected on each patient included age, ethnicity, type of glaucoma, intraocular pressure (IOP), glaucoma medications, and previous laser or incisional surgery. The data collected on each follow-up visit included IOP by Goldmann applanation tonometry with correction for central corneal thickness and glaucoma medications. The minimum postoperative follow-up was 6 months. Outcome was based on the IOP of the last follow-up visit or prior to additional glaucoma surgery.

Success was arbitrarily defined as a final IOP between 7 and 17 mmHg with or without the need for glaucoma medication, while eyes with an IOP under 7 mmHg were defined as hypotony, and those over 17 mmHg or those that underwent additional glaucoma surgery were defined as hypertension. The patients were divided according to success, hypotony or hypertension outcome. The hypotony and hypertension groups were each compared to the success group for statistical differences with regard to MMC concentration and exposure time, as well as age, gender, ethnicity, glaucoma type, preoperative IOP and prior surgery, using the proportional hazard Cox regression model for multivariate analysis.

Results

A total of 155 eyes of 155 consecutive patients who underwent trabeculectomy with adjunctive MMC were included in the study. Patient characteristics and preoperative data are shown in Table 2. The mean patient age was 65.4 years (range, 18–89 years) and eighty-five (54.8%) were female. Thirty-two patients (20.6%) were black and 123 (79.4%) were nonblack. One hundred and twenty nine patients (83.2%) had chronic open-angle glaucoma, and the other forms of glaucoma included 8 (5.2%) chronic angle-closure, 9 (5.8%) pseudoexfoliation, 3 (1.9%) uveitic, 2 (1.3%) juvenile, and 4 (2.6%) miscellaneous types. Of the 155 eyes, 62 (40.0%) had undergone prior argon laser trabeculoplasty and 44 (28.4%) had previous failed trabeculectomy. Cataract

Table 2 Patient characteristics and preoperative data of total study population

Variable	Total
Age (years)	
mean ± SD*	65.36 ± 15.40
range	18 to 89
Gender	
male	70 (45.2%)
female	85 (54.8%)
Ethnicity	
black	32 (20.6%)
nonblack	123 (79.4%)
Glaucoma type	
COAG†	129 (83.2%)
other	26 (16.8%)
Previous surgery	
trabeculectomy	44 (28.4%)
ALT‡	62 (40.0%)
cataract	43 (27.7%)
Preoperative IOP§ (mmHg)	
mean ± SD*	24.02 ± 8.98
range	10 to 65
Preoperative medications	
0–2	74 (47.7%)
3 or more	81 (52.3%)

Notes: *SD, standard deviation; †COAG, chronic open-angle glaucoma; ‡ALT, argon laser trabeculoplasty; §IOP, intraocular pressure.

extraction had been previously performed in the study eye of 43 (27.7%) patients. The mean preoperative IOP was 24.0 ± 9.0 mmHg and 81 patients (52.3%) were on 3 or more medications in the study eye. The mean follow-up was 15.1 months with a range of 6 to 31 months.

The mean final IOP for all patients was 12.6 ± 6.1 mmHg, with 119 (76.8%) classified as success, 21 (13.5%) as hypertension and 15 (9.7%) as hypotony. The preoperative and surgical data for the success, hypotony, and hypertension groups are summarized in Table 3, and the postoperative data are summarized in Table 4.

Of the 119 patients who were defined as having a successful outcome, the mean preoperative IOP was 23.2 ± 9.2 mmHg and 63 patients (52.9%) were on 3 or more medications in the study eye. The mean final IOP in this outcome group was 11.7 ± 2.9 mmHg, and 8 (6.7%) required 3 or more medications postoperatively. Of the 21 patients in the hypertension group, the mean preoperative IOP was 29.1 ± 7.1 mmHg and 12 patients (57.1%) were on 3 or more medications. The mean final IOP was 23.6 ± 7.1 mmHg and all were on maximum tolerable medical therapy. Of the 15 patients in the hypotony group, the mean preoperative IOP was 23.4 ± 7.7 mmHg, and 6 patients (40.0%) were on 3 or more medications. The mean final IOP was 4.4 ± 1.5 mmHg, with no patients receiving medical therapy. Outcomes were not influenced by the presence or type of cataract surgery nor by the refractive status of the patients.

Multivariate analysis, comparing the success and hypotony groups, revealed no statistically significant difference with regard to MMC concentration or exposure time, gender, ethnicity, glaucoma type, preoperative IOP, or previous surgery. However, there was a statistically significant difference with regard to age, in that the mean age of the hypotony group was 73.5 ± 6.1 years compared to 65.6 ± 15.2 years in the success group ($p = 0.009$).

The analysis comparing the success and hypertension groups revealed no statistically significant difference with regard to MMC protocol or any patient variables.

Discussion

In 1983, Chen[1] was the first to report the clinical use of intraoperative MMC as an adjunct to glaucoma filtering surgery. Although subsequent studies have supported the beneficial effects of MMC on postoperative IOP reduction and filtration bleb survival, the benefit has been tempered by associated complications, including hypotony maculopathy. There is a considerable body of literature addressing the quest for a protocol that best balances the benefits and risks of intraoperative MMC as an adjunct to trabeculectomy, a portion of which is summarized in Table 5.

An important question in this search for the ideal protocol has been whether a single protocol is suitable for all patients, or whether the protocol should be titrated for individual patients. The two variables that have received the most attention in evaluating protocols are concentration and exposure time of the MMC. Early studies used fixed concentrations of 0.2–0.5 mg/ml for 3–5 minute exposures and revealed uniformly high success rates with regard to IOP control and low rates of hypotony.[1,3–7] Although these studies were primarily in patients who were at high risk of failure due to excessive fibrosis, other investigators have performed initial trabeculectomies in lower risk patients, using similar, fixed protocols to those described above, and also reported high success with low rates of hypotony.[8,9]

In some studies, different concentrations of MMC were arbitrarily assigned to patients, while the exposure time was kept constant in all patients.[2,17–18] In each study, patients

Table 3 Comparison of preoperative and surgical data for hypertension and hypotony outcome groups against success group

Variable	Success*	Hypertension†	p value	Hypotony‡	p value
No of eyes	119	21		15	
Age (years)			0.132		0.009
mean ± SD§	65.62 ± 15.24	58.05 ± 17.95		73.53 ± 6.16	
range	18 to 89	19 to 82		61 to 82	
Gender§			0.376		0.239
male	56 (47.1%)	7 (33.3%)		7 (46.7%)	
female	63 (52.9%)	14 (66.7%)		8 (53.3%)	
Ethnicity§			0.828		0.156
black	26 (21.8%)	5 (23.8%)		1 (6.7%)	
non-black	93 (78.2%)	16 (76.2%)		14 (93.3%)	
Glaucoma type§			0.168		0.597
COAG††	102 (85.7%)	15 (71.4%)		12 (80.0%)	
other	17 (14.3%)	6 (28.6%)		3 (20.0%)	
Previous surgery¶			0.164		0.179
trabeculectomy	32 (26.9%)	6 (28.6%)		6 (40.0%)	
ALT‡‡	46 (38.7%)	8 (38.1%)		7 (46.7%)	
cataract	30 (25.2%)	8 (38.1%)		5 (33.3%)	
Preoperative IOP§§ (mmHg)			0.280		0.595
mean ± SD**	23.20 ± 9.19	29.10 ± 7.08		23.40 ± 7.67	
range	10 to 65	19 to 48		15 to 44	
Preoperative medications*			0.120		0.451
0–2	56 (47.1%)	9 (42.9%)		9 (60.0%)	
3 or more	63 (52.9%)	12 (57.1%)		6 (40.0%)	
MMC concentration (mg/ml)			0.443		0.185
mean ± SD**	0.25 ± 0.08	0.28 ± 0.09		0.29 ± 0.08	
range	0.2 to 0.4	0.2 to 0.4		0.2 to 0.4	
MMC duration (minutes)			0.891		0.085
mean ± SD**	2.69 ± 0.84	2.88 ± 1.04		3.03 ± 0.88	
range	1 to 5	2 to 5		1 to 4	

*Success, 7–17 mmHg; †Hypertension, >17 mmHg; ‡Hypotony, <7mmHg; §Percentage, ratio of the two variables; ¶Percentage, % of the total in that group; **SD, standard deviation; ††COAG, chronic open-angle glaucoma; ‡‡ALT, argon laser trabeculoplasty; §§IOP, intraocular pressure.

receiving the higher concentration were more likely to develop hypotony.

Other studies have examined the impact of variable exposure times with MMC. An *in vitro* study by Jampel[19] showed that a 1-minute exposure of MMC may be as effective as a 5-minute exposure for inhibition of Tenon's fibroblast proliferation. In clinical trials, in which a fixed concentration of MMC was titrated from 0.5 to 5 minutes exposure time, according to individual patient's risk factors for failure from excessive fibrosis, some studies also revealed no correlation with exposure time and either success of IOP control or risk of hypotony,[10,11,20] while others showed a higher incidence of hypotony in eyes receiving the longer exposure time.[21,22]

In two clinical trials, the MMC concentration was kept constant at 0.3 or 0.4 mg/ml, and the exposure time was titrated between 2–3 minutes or 4–5 minutes, based on risk factors for surgical failure.[12,13] In both series, hypotony maculopathy occurred more in the lower risk patients, who received the shorter duration of exposure. The authors interpreted these findings to suggest that individual patient factors had a greater influence on the outcome than the exposure time of the MMC.

Other investigators have varied both concentration and exposure time according to risk of surgical failure, as was utilized in the present study. In two of these studies, which compared 0.5 mg/ml for 5 minutes with 0.4 mg/ml for 3 minutes[14] and 0.2–0.5 mg/ml for 0.5–5 minutes,[15] neither study revealed

Table 4 Comparison of postoperative data for hypertension and hypotony groups against success group

Variable	Success*	Hypertension†	Hypotony‡
Final IOP¶ (mmHg)			
mean ± SD§	11.65 ± 2.86	23.57 ± 7.10	4.40 ± 1.45
range	7 to 17	18 to 48	1 to 6
Postoperative medications**			
0–2	111 (93.3%)	17 (81.0%)	0
3 or more	8 (6.7%)	4 (19.0%)	0
Mean follow-up (mos)	15.21 ± 7.10	14.33 ± 6.28	15.07 ± 6.60
range	6 to 31	6 to 27	6 to 30

Notes: *Success, 7–17 mmHg; †Hypertension, >17 mmHg; ‡Hypotony, <7 mmHg; §SD, standard deviation; ¶IOP, intraocular pressure; **Percentage, ratio of the two variables.

a correlation between MMC variables and IOP outcome. A third study compared protocols of 0.2 mg/ml for 2 minutes, 0.2 mg/ml for 4 minutes, 0.4 mg/ml for 2 minutes, or no MMC and found a possible dose-response relationship, with exposure time appearing to be more important than concentration.[16]

In the present study, we divided patients into three outcome groups: success (IOP of 7–17 mmHg with or without glaucoma medication); hypotony (IOP less than 7 mmHg); and hypertension (IOP greater than 17 mmHg or requiring further glaucoma surgery), and examined whether either MMC variable or certain patient variables correlated with the outcome groups. The only significant variable was age, with the hypotony group having an older mean age than the success group. This finding is consistent with prior observations that younger patients are generally at greater risk of filtration surgery failure,[23] and suggests that older patients require less, if any, MMC during trabeculectomy. On the other hand, younger patients are also at greater risk of developing maculopathy from hypotony,[24,25] making it difficult to select the optimum MMC protocol, especially in young patients.

The clinical investigations cited in this paper, including our study, do not provide clear support for the superiority of a titration protocol for MMC as an adjunct to trabeculectomy, compared to a fixed protocol for all patients. While some studies suggest that higher concentrations and/or longer exposure times may increase the success of IOP control, but also increase the risk of hypotony,[2,17,18] the majority of studies show no correlation between either MMC variable and the surgical outcome. There may be several explanations for the latter observation.

First, some studies only included patients who were at high risk of failure from excessive fibrosis, so that a single, fixed protocol might have been appropriate for the majority of these patients. In those studies in which the patient population represented a wider range of risk for surgical failure, and MMC variables were titrated, as in the present study, the lack of correlation between MMC variables and surgical outcome might be interpreted to suggest that other patient variables were responsible for the hypertension and hypotony outcomes. In other words, with a less appropriate MMC protocol, the concentration or exposure time might have been significantly higher in the hypotony group and lower in the hypertension group. It is just as likely, however, that the lack of correlation between MMC protocol and IOP outcome represents an inappropriate combination of all the surgical and patient variables.

Our study is limited by the retrospective study design. In addition, it is difficult to extrapolate our results to that of others, because of many variations in surgical technique. For example, while we applied MMC before development of the scleral flap, other surgeons apply the MMC beneath the scleral flap. These and other variations in surgical technique could influence the outcome of trabeculectomy beyond the influence of the concentration and duration of MMC application.

It seems most reasonable to conclude from the studies cited in this paper that the IOP outcome following trabeculectomy with adjunctive MMC represents a complex interaction of many surgical and patient variables. In addition to the concentration and exposure time of MMC, the vehicle used to deliver the MMC and the surgical placement of the vehicle, as well as all the other steps in the operation, may well influence the outcome. There may also be patient variables, beyond those evaluated in the present study, such as the thickness of Tenon's capsule, the degree of vascularity and bleeding, and possibly different receptor responses to MMC, that exert an influence on the surgical outcome.

While no claims can be made for the superiority of any specific MMC protocol in overcoming this complex problem, the findings in the present study and a review of the literature are felt to support the merit of carefully evaluating the risk factors of each individual patient and selecting the surgical approach, including the use of antifibrotic agents, that is felt to be most appropriate for that patient.

Disclosure

This study was presented as a poster at the American Ophthalmologic Society Annual Meeting, Half Moon Bay, California, May 21–24, 2006. This study was performed at the Department of Ophthalmology and Visual Science, Yale University School of Medicine,

Table 5 Summary of literature evaluating mitomycin C (MMC) as an adjunct to trabeculectomy

Authors	Number of eyes	Duration of follow-up (months)	MMC concentration (mg/ml)	MMC duration (minutes)	Results	
					Success	Hypotony (eyes)
Kitazawa et al 1991	17	7 to 12	0.2	5	88%	0
Skuta et al 1992	20	6	0.5	5	95%	1
Katz et al 1995	20	26 to 38	0.5	5	81.3%	1
Palmer 1991	33	6 to 42	0.2	5	84%	1
El Sayyad et al 2000	68	12	0.3	3	71%–82%	4
Nuijts et al 1997	25	12	0.2	5	92%	1
Scott et al 1998	89	24	0.5	5	85%	4
Kitazawa et al 1993	22	6 to 17	a) 0.2	a) 5	100%	2
			b) 0.02	b) 5	63.6%	0
Sanders et al 1999	50	12	a) 0.2	a) 2	72.0%	2
			b) 0.4	b) 2	70.8%	3
Chen et al 1990	59	12 to 76	0.1–0.4	5	77.8%	2
Cohen et al 1997	106	14	a) 0.5	a) 0.5–1	*	1
			b) 0.5	b) 1–3		4
Perkins et al 1998	68	36	0.5	0.5–5	*	3
Shields et al 1993	59	2 to 14	a) 0.4	a) 2–3	91.2%	4
			b) 0.4	b) 4–5	72.2%	0
Stone et al 1998	57	11.9	a) 0.3	a) 1–3	*	3
			b) 0.3	b) 4–5		0
Megevand et al 1995	73	18	a) 0.2	a) 2	88%	2
			b) 0.2	b) 5	84%	1
Kim et al 1998	88	3 to 12	a) 0.5	a) 0.5–1	†	29
			b) 0.5	b) 3–5		20
Zacharia et al 1993	52	2 to 12	0.4	3.5–7	†	17
Neelakantan et al 1994	93		a) 0.4	a) 3	*	
			b) 0.5	b) 5		
Cheung et al 1997	157	36	0.2–0.5	0.5–5	*	
Robin et al 1997	300	12	a) 0.2	a) 2	79.4%	2
			b) 0.2	b) 4	83.3%	2
			c) 0.4	c) 2	85.7%	2

Notes: *No correlation between MMC variable and outcome; †Statistically significant association between MMC variable and outcome.

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