Protocol for mitomycin C use in glaucoma surgery

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ABSTRACT.

Purpose: **To evaluate the results of a protocol described for mitomycin C (MMC) use in trabeculectomy or combined surgery (phacoemulsification and trabeculectomy).**

Methods: **A total of 143 eyes (60 trabeculectomies and 83 combined surgeries) of 124 patients were divided into four groups: group 1 (without MMC); group 2 (with 0.1 mg/ml MMC); group 3 (with 0.2 mg/ml MMC), and group 4 (with 0.4 mg/ml MMC). Two-minute MMC was used in every case in groups 2, 3 and 4. The results were analysed after 1 year of follow-up. Intraocular pressure (IOP) and complications were evaluated. Successful IOP control was defined when IOP was <21 mmHg and <16 mmHg if advanced glaucoma was present, always without additional medical treatment.**

Results: **Mean preoperative IOP decreased from 24.60 mmHg (SD 1.40 mmHg) to 13.47 mmHg (SD 0.37 mmHg) ($p < 0.00001$), 12 months postoperatively. Control in IOP was achieved in 79.02% of eyes. No significant differences were found in final mean IOP values ($p > 0.196$) or in postoperative complications ($p > 0.120$) in groups 2, 3 and 4.**

Conclusion: **With the protocol described, a selection of concentration of MMC has been made in different clinical forms of glaucoma. No significant differences in IOP control and postoperative complications were noticed among the groups.**

Key words: mitomycin C – trabeculectomy – intraocular pressure – postoperative complications

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Introduction

The introduction of mitomycin C (MMC) for glaucoma surgery in the early 1990s increased the success rate of trabeculectomy, although more frequent complications have been reported (Kupin et al. 1995; Cohen et al. 1996; Costa et al. 1996; Rockwood et al. 2000; Casson & Salmon 2001; Membrey et al. 2001; Mwanza & Kabasele 2001).

Trabeculectomy with adjunctive MMC is the most widely accepted filtering surgery for surgical treatment of glaucoma (Chen et al. 1997). However, controversy exists with regard to optimum MMC concentration, exposure time, delivery vehicle and the size or shape of the sponge (Chen et al. 1997; Singh 1997).

Extreme care must be taken with the use of adjunctive MMC. Every surgeon should develop his or her own experience with particular parameters in order to obtain better results and fewer complications. In this article, the results obtained with trabeculectomy and combined surgery are described, according to a protocol designed for the use of MMC at three different concentrations.

Material and Methods

A prospective, non-randomized study was performed. A total of 143 eyes of 124 patients who had undergone primary trabeculectomy or combined surgery between February 2000 and April 2002 were included in this study. All patients were white, with a median age of 66.85 years (SD 1.40 years). Seventy-six (61.20%) female and 48 (38.70%) male patients were included. Patients with different types of glaucoma were enrolled (Table 1), most of them with primary open-angle glaucoma (77.62%). All of them had medically uncontrolled glaucoma, with progression of campimetric lesions or cup : disc ratio.

The preoperative ophthalmic examination included best corrected visual acuity (VA), biomicroscopy, gonioscopy, tonometry with a Goldmann applanation tonometer, indirect ophthalmoscopy, cup : disc ratio and automated perimetry (initially with Octopus Program G1; finally with Humphrey Program 24–2 test).

All surgeries were performed by the same surgeon (JAM). A standard limbus-based conjunctival flap and a scleral flap of 5 × 5 mm was made out in all cases. When cataract surgery was

Table 1. Clinical forms of glaucoma included in the study.

	Eyes (*n*)
Chronic open-angle glaucoma	111
Chronic angle-closure glaucoma	12
Glaucoma in aphakia	7
Pseudoexfoliative glaucoma	3
Glaucoma associated with ocular trauma	3
Glaucoma associated with uveitis	3
Pigmentary glaucoma	1
Pupillary block glaucoma	1
Glaucoma associated with elevated episcleral venous pressure	1
Congenital glaucoma	1

indicated, phacoemulsification with a foldable intraocular lens was performed. When necessary, a 3×5 mm piece of sponge (Espongostan Film, Ferrosan A/S, Copenhagen, Denmark) soaked with MMC was placed under the conjunctival flap over the scleral bed for 2 min. Subsequently, the sponge was removed and the space between the flap and episclera was copiously irrigated with balanced salt solution. The concentration of MMC was determined according to the protocol established by the Department of Ophthalmology of the University Hospital of Valladolid, in which different values were assigned according to the risk factors of every patient (Table 2). In advanced glaucoma (Weitzman & Caprioli 1996), target intraocular pressure (IOP) was considered to be <16 mmHg. The risk factors most frequently observed included previous use of medical topical anti-glaucoma medications for longer than 1 year (101 eyes), combined surgery (83 eyes) and advanced glaucoma (68 eyes). Although 101 eyes (70.62%) had a cup : disc ratio >0.7, only 68 (47.5%) presented advanced campimetric lesions and were included in this last group (Table 3).

Table 2. Protocol to select MMC concentration.

Risk factor	Assigned risk
Previous surgery (conjunctiva)	6
Combined surgery	5
Secondary glaucoma	4
Target IOP <16 mmHg	4
Topical treatment >1 year	3
Age <40 years	3
Diabetes mellitus	1
Previous laser trabeculoplasty	1
Assigned risk	**MMC concentration**
<2	No MMC
3–5	0.1 mg/ml
6–9	0.2 mg/ml
>10	0.4 mg/ml

According to this protocol, four groups were characterized: no MMC, or application of MMC at concentrations of 0.1, 0.2 or 0.4 mg/ml. The scleral flap was closed with four to five 10–0 monofilament nylon sutures. Tenon's capsule was then closed with a 10–0 vicryl suture and the conjunctiva with a running 10–0 nylon suture. Following surgery, all patients received topical gentamicin, dexamethasone 1% and atropine 1% drops. Postoperative care included an identical topical medical regimen of dexamethasone 1% and tobramycin 3% at one drop every 2 hours and homatropine 2% ointment every 8 hours for 1 week. Topical dexamethasone had a 6-week tapering period.

The patients were examined 1, 2 and 3 days after surgery; 1, 2 and 3 weeks later, and at 1, 2, 3, 6, 9 and 12 months postoperatively. At the last visit, the preoperative ophthalmic examination was repeated.

In the early postoperative follow-up (up to 3 months), if the IOP was >16 mmHg after intermittent application of digital pressure, laser suture lysis was performed on the scleral flap 10–0 suture with a YAG laser (Visulas 532; Carl Zeiss Jena, Jena, Germany). Successful IOP control was arbitrarily defined as IOP <21 mmHg and <16 mmHg in advanced glaucoma (47.5%), always without additional medical treatment.

Data were analysed statistically using analysis of variance (ANOVA) multiple regression tests (using dummy variables). The level of significance in order to include variables in this model was $\alpha = 0.05$. Statistical tests used for hypothesis contrast were the Student's *t*-test and the chi-squared test. A p-value of < 0.05 was considered significant.

Table 3. Risk factors included in the study.

	Eyes (*n*)	%
Previous surgery (conjunctiva)	12	8.39
Combined surgery	83	58.04
Secondary glaucoma	7	4.89
Target IOP <16 mmHg	68	47.55
Topical treatment >1 year	101	70.62
Age <40 years	2	1.39
Diabetes mellitus	19	13.28

Results

Trabeculectomy was performed in 60 eyes (41.96%) and combined surgery in 83 (58.04%). Only seven eyes did not receive MMC. In the rest of the eyes, MMC at different concentrations was used (Table 4). Mitomycin C at a concentration of 0.2 mg/ml was used most frequently (44.75%). All patients were followed-up for a period of 12 months.

Mean preoperative IOP was 24.60 mmHg (SD 0.66 mmHg). Mean postoperative IOPs were found to be significantly lower at all time intervals ($p < 0.00001$) (Fig. 1). Mean IOP at 12 months was 13.47 mmHg (SD 0.51 mmHg).

At the end of the follow-up, 128 eyes (89.51%) had IOP <21 mmHg, without medical treatment. As 15 eyes (10.48%) with a target IOP <16 mmHg had IOP >15 mmHg, control of IOP had been achieved without medical treatment in 113 eyes (79.02%).

No significant differences were found in mean IOP at different concentrations of MMC ($p = 0.196$). When MMC was not used, final IOP was higher. However, as fewer eyes were included in this group, the differences were not statistically significant.

To close the scleral flap, a total number of 644 sutures were placed, with a mean of 4.54 (SD 0.09) for each eye. Postoperatively, 221 sutures were cut, with a mean of 1.54 (SD 0.11) for each eye. Sixty-four sutures (28.95%) were cut at days 1 or 2 postoperatively, 112 (50.67%) at week 1 and 194 (87.78%) at month 1.

Mean preoperative VA was 0.29 (SD 0.02, range 0.05–1.25). Mean postoperative VA was 0.50 ($p < 0.05$). This difference was statistically significant

Table 4. Distribution of MMC concentrations.

	Eyes (*n*)	%
No MMC	7	4.90
0.1 mg/ml	37	25.87
0.2 mg/ml	64	44.75
0.4 mg/ml	35	24.48

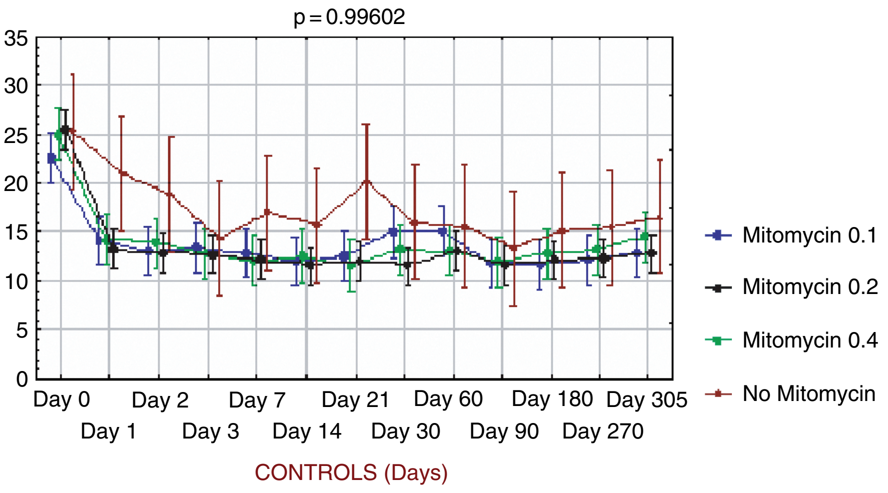

Fig. 1. Mean intraocular pressure (mmHg) at all time intervals. Vertical bars represent 95% CIs.

for eyes undergoing combined surgery (initial VA: 0.13; final VA: 0.56; $p < 0.05$), but not for eyes that underwent trabeculectomy as a single procedure (initial VA: 0.47; final VA: 0.42; $p > 0.05$).

No significant differences in postoperative complications were observed at different concentrations of MMC (Table 5).

Discussion

The size, type and shape of the sponge are known to be important for the efficacy of MMC (Flynn et al. 1995; Mehel et al. 1997). In this study, the characteristics of the sponges did not vary and their size was similar to the size of the scleral flap. It is not known if this size is the most appropriate, but it has been suggested that larger sponges should be avoided because the risk of fistulas increases when blebs are avascular and have a large surface (Hu et al. 2003). Sponges were placed under the conjunctival flap, in a similar way to that described by most authors (Costa et al. 1993; Kupin et al. 1995; Shin et al. 1995; Cohen et al. 1996; Lederer 1996; Rudeerman et al. 1996; Zacharia & Schuman 1997; Lemon et al. 1998; El Sayyad et al. 1999; Ünlü et al. 2000; Casson et al. 2001; Manners et al. 2001). In all cases, sponges were left for 2 min because it has been demonstrated that it is advisable to lower IOP adequately. An *in vitro* study on Tenon's capsule cultures suggests that the effect of MMC would depend mainly on its concentration and it was proved that a sponge placed for 1 min can be as effective as another left for 5 min on inhibition of fibroblasts (Jampel 1992). In clinical studies, it has been observed that with an exposure of 1 min, a tissue becomes saturated with MMC (Zacharia et al. 1993) and that IOP control is similar whether the MMC is used for 2 min or 5 min (Mégevand et al. 1995; Manners et al. 2001). Other authors have found that combined procedures where MMC is administered over 1, 3 or 5 min achieve similar levels of IOP control (Shin et al. 1995), and that prolonged times of application increase the risk of postoperative complications (Zacharia et al. 1993; Cohen et al. 1997; Kim et al. 1998), although there is controversy on this issue (Mégevand et al. 1995).

Of all parameters, the only variable to study was the concentration of MMC. Mitomycin C has been used at approximately 50 different concentrations between 0.01 mg/ml and 0.5 mg/ml (Singh 1997). As Table 2 shows, in order to establish the concentration of MMC, different risk factors described in the ophthalmic bibliography were considered (Prata et al. 1994; Broadway et al. 1995; Shin et al. 1995, 1998; Mietz et al. 1999; You et al. 2002). These factors were selected because they were the most frequently observed in our patients.

In our study, we considered IOP control to be successful when IOP was < 21 mmHg without additional treatment, like most authors (Costa et al. 1993; Belyea et al. 1997; Cohen et al. 1997; Jampel 1997; Zacharia & Schuman 1997; Perkins et al. 1998; Stone et al. 1998).

Fig. 1 shows that postoperative IOP levels were significantly lower than preoperative levels from day 1, and their mean values were lower for 12 months. If the target IOP had been considered as < 21 mmHg in all patients, we would have achieved successful IOP control in 89.51% of the patients, similar to those reported in the literature (Costa et al. 1993; Zacharia et al. 1993; Kupin et al. 1995; Lederer 1996; Mamalis et al. 1996; Belyea et al. 1997; Cohen et al. 1997; Nuijts et al. 1997; Zacharia & Schuman 1997; Perkins et al. 1998; Stone et al. 1998; Caporossi et al. 1999; El Sayyad et al. 2000; Ünlü et al. 2000). However, it is difficult to find similar studies with parameters like MMC, demographics or follow-up times. In our case, one of the risk factors considered to select MMC concentration was advanced glaucoma, in which target IOP was < 16 mmHg (Shin et al. 1996). Sixty-eight patients (47.55%) had advanced glaucoma and IOP control in 15 of them (10.48%) was considered to have failed. With this criterion, after 12 months of follow-up, 113 eyes (79.02%) had achieved successful IOP control without additional treatment.

Table 5. Distribution of postoperative complications and MMC concentration.

Complication	(%)	No MMC	MMC 0.1 mg/ml	MMC 0.2 mg/ml	MMC 0.4 mg/ml	p
Encapsulated bleb	(13.28)	2	4	9	4	0.1213
Shallow anterior chamber	(6.29)	4	2	2	1	0.2312
Cataract	(3.49)	0	3	2	0	0.6923
Choroidal detachment	(10.48)	2	5	4	4	0.3526
Obstruction of fistula by iris	(1.39)	0	0	1	1	1
Endophthalmitis		0	0	0	0	
Fistula	(2.09)	0	3	0	0	
Hyphaema	(11.85)	0	7	9	1	0.7224
Early hypotony	(2.09)	0	1	1	1	0.4621
Late hypotony	(1.39)	0	0	1	1	
Hypotony maculopathy	(0.69)	0	1	0	0	

Mean IOP values at different MMC concentrations (Fig. 1) were similar in all three groups in which MMC was used. These results did not differ from those obtained by Sanders et al. (1999), and we can conclude that the present protocol was useful for selecting different MMC concentrations according to several risk factors. The group of patients in which MMC was not used had higher IOP levels, similarly to other studies (Kupin et al. 1995; Cohen et al. 1996; Rockwood et al. 2000; Casson & Salmon 2001; Membrey et al. 2001; Mwanza & Kabasele 2001). However, because of the small number of patients in this group, the differences were not significant.

There were not significant differences in the number of complications and IOP control in the four groups of patients in the study. These results can be explained because the established risk factors allowed us to select the MMC concentration adequately. The most frequent complication was encapsulated filtering blebs (13.28%), similar to that found by Prata et al. (1995), but higher than that of other studies on MMC use (Kupin et al. 1995; Mégevand et al. 1995; Singh et al. 2000). In our series, we found choroidal detachments in 10.48% of eyes, which is lower than other percentages described in the literature (Costa et al. 1996; Rasheed 1999). We observed hyphaema in the early postoperative stage in 11.88% of eyes, while other authors have described frequencies of 7.8–28% (Costa et al. 1993; Prata et al. 1995; Rudeerman et al. 1996). Three cases of early hypotony (2.09%) were observed because of overfiltration and required surgical closure. We found two cases of late hypotony (1.39%) in eyes with cystic blebs, probably related to tisular bleb disruption, although a toxic effect of MMC over the ciliary body cannot be ruled out (Nuyts et al. 1994). This percentage is similar to another described with trabeculectomy (Kim et al. 1998; Mietz & Krieglstein 1998; Mietz et al. 2000), although it is not easy to compare because there are differences in the parameters of MMC use and types of glaucoma. Furthermore, there is no agreement in the definition of hypotony (Zacharia et al. 1993; Shin et al. 1995; Rudeerman et al. 1996; Mehel et al. 1997; Lemon et al. 1998; El Sayyad et al. 2000; Bindlish et al. 2002). Although some researchers consider that this complication is not related to MMC exposure time or MMC concentration (Bindlish et al. 2002), others observe hypotony more frequently with a longer MMC exposure time (Kim et al. 1998) or with higher MMC concentrations (Kitazawa et al. 1993). Similarly, we found late fistulas in three eyes (2.09%), while other authors have described 14.60% in 5 years of follow-up (Bindlish et al. 2002). Postoperative complications were not more frequent when a higher concentration of MMC was used, in contrast to the results found by other researchers (Kitazawa et al. 1993; Sanders et al. 1999).

A weakness of the study is that the MMC dose was related to several risk factors, which makes it difficult to compare both the effects of MMC dose or the success rates of patients with similar risk factor profiles. In addition, the study lacked a control group of patients with risk factors without MMC use. However, several authors have demonstrated that MMC use improves IOP control in these cases (Cohen et al. 1996; Costa et al. 1996; Casson & Salmon 2001; Mwanza % Kabasele 2001).

In summary, with this protocol we selected an adequate concentration of MMC for every patient, which allowed us to control IOP at similar levels for different groups. No significant correlation between the number of complications and MMC concentration was found.

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