ORIGINAL ARTICLE

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Comparison of outcomes of trabeculectomies using 0.4 mg/ml versus 0.2 mg/ml concentrations of mitomycin-C

ABSTRACT

Objectives

This study compared the outcomes of trabeculectomies using 0.2 mg/ml and 0.4 mg/ml mitomycin-C (MMC) and determined the factors that can predict the postoperative intraocular pressure (IOP).

Methods

A prospective, randomized, comparative study was performed involving patients undergoing trabeculectomy who were randomly assigned to either 0.2 mg/ml MMC for 4 minutes or 0.4 mg/ml for 2 minutes. The IOP, bleb characteristics, and occurrence of complications were compared. Age and gender of the patients, preoperative IOP, MMC concentration, bleb characteristics, angle status, and age of the surgery were analyzed to determine if they are predictive factors of the postoperative IOP using univariate and multivariate analyses.

Results

Seventy-four eyes of 68 patients underwent trabeculectomy: 36 eyes were treated with 0.2 mg/ml MMC for 4 minutes and 38 eyes with 0.4 mg/ml MMC for 2 minutes. There was no statistically significant difference in the mean preoperative IOP and postoperative IOP, as well as in the mean percent change in IOP ($p = 0.87$) between the 2 groups. Univariate and multivariate analyses showed the preoperative IOP ($p = 0.02$) and the type of filtering bleb (cystic $p < 0.001$; diffuse $p = 0.045$) as predictive factors of postoperative IOP. Kaplan-Meier survival curves showed no significant difference between the 2 groups at an average follow-up of 20 weeks.

Conclusion

There is no significant difference in the outcomes of trabeculectomies using 0.2 mg/ml and 0.4 mg/ml MMC. Preoperative IOP and bleb characteristics are factors predictive of successful filtration surgery.

Key words: *Trabeculectomy, Mitomycin-C, Intraocular pressure, Filtering bleb*

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THE SURGICAL management of glaucoma is an indispensable alternative in developing countries where there are limitations in medical and laser therapy. Glaucoma filtration surgery fails due to the scarring of the filtering bleb, where fibroblast proliferation from the episclera and Tenon's capsule play a significant role.[1] The use of antimetabolites has improved the success rate of glaucoma filtration surgery. Mitomycin-C is an antibiotic with antineoplastic activity, inhibiting the proliferation of fibroblasts. At present, there is no known consensus as to the ideal concentration and exposure time of mitomycin-C.[2-17] The concentrations used in different studies ranged from 0.02 mg/ml to 0.5 mg/ml. The most commonly used concentrations are 0.2 mg/ml and 0.4 mg/ml. Exposure time varies from 30 seconds to 5 minutes, with the latter as the most common.

This study compared the outcome of trabeculectomies using 0.4 mg/ml MMC (Mitomycin C Kyowa, Tokyo, Japan)for 2 minutes as against 0.2 mg/ml MMC for 4 minutes in terms of IOP lowering, characteristics of the filtering bleb, and incidence of complications. It also determined the factors that can predict the postoperative intraocular pressure (IOP).

METHODOLOGY

Patients seen consecutively at the Glaucoma Service of the Philippine General Hospital (PGH) between January and June 1997 were evaluated. Those who had uncontrolled IOPs, cup-disc ratio of 0.8 or worse, and on maximum tolerated medical therapy were eligible for inclusion into the study. Patients who had systemic contraindications to surgery, who could not comply with the follow-up schedule, or who refused to give their consent were excluded.

Based on the clinical diagnosis, patients requiring a filtering procedure were classified as either low risk for surgical failure (e.g. primary glaucomas) or high risk for surgical failure (e.g. congenital and developmental glaucomas, neovascular glaucoma, previous surgeries, failure of previous trabeculectomy, traumatic glaucoma, previous cataract surgery, secondary glaucoma, inflammatory glaucoma).[18] Using a table of random values, each patient was assigned to either the 2 minute exposure of 0.4 mg/ml MMC or the 4 minute exposure of 0.2 mg/ml MMC. The patients and the surgeons were masked as to which MMC concentration would be used. A trabeculectomy protocol approved by the consultants of the Glaucoma Service was used.

After peribulbar anesthesia was given, a corneal bridle using vicryl 8-0 (Ethicon, Johnson & Johnson International, New Brunswick, NJ, USA), was sutured at 12:00. A superior limbal-based conjunctival flap 10 mm posterior to the limbus was created. After hemostasis and clearing of the episclera, a 3x3 mm triangular scleral flap of half thickness was fashioned with the apex of the flap at 12:00. The flap was dissected anteriorly up to the limbal gray zone. A 3mm cut cotton sponge soaked in MMC was applied under the scleral flap. Only the assisting resident was aware of the actual exposure time and was in charge of removing the cotton sponge from the surgical field. The scleral bed was irrigated with 40 ml of balanced salt solution. A paracentesis was done at the temporal limbus and its patency tested. The anterior chamber was entered using blade 11 knife and a sclerostomy was created with 0.75 mm Kelly punch (Storz, St. Louis, MO, USA). Peripheral iridectomy was done with Vannas scissors. The anterior chamber was reformed and the filtering of fluid checked. Three 10-0 nylon sutures secured the scleral flap snugly to the scleral bed; fluid was seen to egress after lightly dabbing on the incision site with a cotton pledget. The Tenon's capsule and conjunctiva were sutured continuously and closed separately with nylon 10-0 suture. All surgeries were performed by the glaucoma fellow and the 7 senior residents who were rotating in the Glaucoma Service during that period.

The IOP before surgery and on the most recent follow-up were compared. The main outcome measure was the change in IOP. The filtering surgery was considered successful when there was at least 30% reduction of IOP from baseline. Secondary outcome measures were the type of filtering bleb and incidence of complications. The type of filtering bleb on the most recent follow-up was classified:

- cystic, if the bleb was localized, elevated, with cystic changes of the overlying conjunctiva;
- diffuse, if the border of the bleb was ill-defined, elevated with no visible changes in the overlying conjunctiva;
- vascular or congested, if the bleb was localized, elevated, and surrounded by ropy blood vessels; or
- flat, if the bleb is not elevated, difficult to discern (not visible), and there were no changes to the overlying conjunctiva.

The outcome assessors were masked as to the patient's group assignment.

Univariate and multivariate analyses using Cox proportional hazard modeling were done to determine the effects of factors such as age and gender of the patient, angle status, preoperative IOP, MMC concentration and duration in minutes of MMC application, bleb characteristics, and age of the surgery or duration of follow-up on the postoperative IOP. For variables age and sex, the unit of analysis was based on the patient for person-based covariates. For the other variables studied, the unit was based on the eye for eye-based covariates. Kaplan-Meier survival curves were determined for the two treatment groups to detect any difference in IOP change over the period of follow-up.

Table 1. **Distribution of patients according to risk of surgical failure and MMC concentration.**

Diagnosis	Risk	MMC Concentration	
		0.2 mg/ml	0.4 mg/ml
Primary open-angle glaucoma	Low	4	3
Chronic angle-closure glaucoma	Low	17	15
Intermittent angle-closure glaucoma	Low	2	2
Acute angle-closure glaucoma, refractory	Low	1	2
Neovascular glaucoma	High	2	3
Failed trabeculectomy	High	2	3
Developmental glaucoma	High	0	5
s/p Cataract extraction (ECCE) with PCIOL	High	1	1
s/p Combined surgery	High	0	2
Axenfeld-Rieger syndrome	High	4	0
Secondary angle-closure glaucoma	High	0	2
Previous intraocular surgery (other than cataract surgery)	High	3	0
TOTAL		**36**	**38**

Table 2. **Comparison of mean preoperative and postoperative IOPs in eyes treated with 0.2 mg/ml and 0.4 mg/ml MMC.**

Treatment Group	Preoperative	Postoperative	Mean IOP Reduction (mm Hg)[c]	Mean % change
0.2 mg/ml	37.5 ± 13.2	14.0 ± 7.9[a]	-18.1	-49.4 ± 6.6
0.4 mg/ml	34.4 ± 12.0	15.6 + 8.4[b]	-17.4	-42.9 ± 6.6

[a]p = 0.002, [b]p = 0.038, [c]p = 0.873

Table 3. **Distribution of types of filtering bleb and mean IOP change.**

Bleb Type	Fre-quency	0.2 mg/ml MMC	0.4 mg/ml MMC	Mean IOP Change	95%Confidence Interval	
					Lower	Upper
Cystic	45	22 (61%)	23 (61%)	-22.575 ± 2.086	-26.744	-18.407
Diffuse	9	4 (11%)	5 (13%)	-21.152 ± 2.798	-26.740	-15.563
Vascular	9	6 (17%)	5 (13%)	-7.435 ± 2.922	-13.272	- 1.598
Flat	11	4 (11%)	5 (13%)	-19.918 ± 2.974	-25.859	-13.977

Table 4. **Factors predictive of postoperative IOP (univariate analysis).**

Factors Studied	Hazard Ratio	95% Confidence Interval		*p* Value
		Lower	Upper	
Age of patient	-5.730	-5.818	-5.642	0.211
Preoperative IOP	-0.960	-1.093	-0.827	<0.001
Diffuse bleb	-12.765	-19.233	-6.297	<0.001
Vascular bleb	-11.819	-18.293	-5.345	0.001
Cystic bleb	-14.621	-19.987	-9.255	<0.001
Mitomycin	0.541	-2.683	3.765	0.743
Neovascular glaucoma	1.295	-6.090	8.680	0.732
Duration of follow-up	8.303	8.158	8.448	0.269

Table 5. **Factors predictive of postoperative IOP (multivariate analysis).**

Factors Studied	Hazard Ratio	95% Confidence Interval		1/Exp (B)*	*p* Value
		Lower	Upper		
Mitomycin C	0.271	-0.968	1.510	0.763	0.668
Age of patient	-0.005	-0.038	0.028	1.005	0.749
Diffuse bleb	-1.932	-3.818	-0.046	6.897	0.045
Vascular bleb	-0.549	-2.323	1.225	1.730	0.544
Cystic bleb	-3.201	-4.632	-1.770	24.390	<0.001
Angle closure	-0.254	-1.777	1.269	1.289	0.744
Neovascular glaucoma	1.865	-0.838	4.568	0.155	0.176
Preoperative IOP	-0.121	-0.223	-0.019	1.129	0.020

*odds ratio

RESULTS

A total of 74 eyes of 68 patients (46 females, 22 males; mean age of 51 ± 2.2 years) underwent filtering surgery between January and June 1997. Forty-three (58.1%) of these eyes were right eyes.

Forty-six eyes were classified as low risk and 28 eyes as high risk (Table 1). The two MMC concentrations studied were evenly distributed between the two surgical risk groups. Thirty-six eyes were treated with 0.2 mg/ml MMC while 38 eyes were treated with 0.4 mg/ml MMC. The mean preoperative IOP was 35.9 ± 1.47 mm Hg and the mean postoperative IOP was 14.8 ± 0.94 mm Hg (Table 2). The mean IOP change for both groups from preoperative levels was –21.1 ± 1.8 mm Hg. There was no statistically significant difference (p = 0.87) in mean IOP reduction between the two groups postoperatively (Table 2). The average percent change in IOP was –53.8 ± 3.3 for both groups. Fifty-five eyes (74.3%) achieved a 40% reduction from baseline IOP. Fifty-eight eyes (78.4%) achieved a 30% reduction from baseline IOP. The mean follow-up period was 19.7 ± 1.5 weeks.

The most common bleb in both treatment groups was cystic (Table 3). There was no difference in the type of bleb between the 2 groups. The different bleb types also showed differences in postoperative IOP. Flat bleb had the lowest IOP change of only 7.435 mm Hg compared to 21.152 mm Hg for diffuse bleb, 19.918 mm Hg for vascular bleb, and 22.575 mm Hg for cystic bleb (Table 3).

Complications noted were few: 3 cases of hypotony (2 in 0.2 mg/ml and 1 in 0.4 mg/ml), 4 cases of hyphema (1 in 0.2 mg/ml and 3 in 0.4 mg/ml), 1 case of flat anterior chamber (0.4 mg/ml) and 2 cases of choroidal effusion (0.2 mg/ml). There was no difference in the incidence of complications between the two groups.

Univariate analysis showed that preoperative IOP and the different types of bleb are significant predictors of IOP after filtering surgery (Table 4). In multivariate analysis, only preoperative IOP, cystic and diffuse blebs are significant predictors of postoperative IOP (Table 5). There is no evidence that MMC concentration (either the 0.2 mg/ml or the 0.4 mg/ml concentration), angle configuration, patient age, patient gender, age of the surgery in weeks are predictors of IOP after filtering

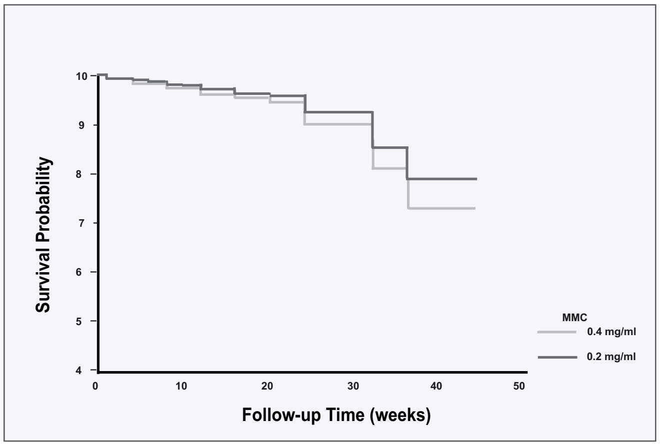

Figure 1. Kaplan-Meier survival curve of 0.2 mg/ml and 0.4 mg/ml MMC.

surgery (Table 4). Linear regression analysis showed that for every 1 mm Hg IOP rise at baseline, there is a corresponding 0.960 mm Hg reduction in IOP during the postoperative follow-up. The regression model has an R^2 of 82%, indicating that the variability of the IOP after filtering surgery is explained by the identified independent variables in the model 82% of the time.

Figure 1 shows the survival curves of the two treatment groups. The difference in survival between the groups is not statistically significant.

DISCUSSION

Mitomycin-C is one of the most frequently used antifibrotic agents in glaucoma filtration surgery. In conditions where the incidence of bleb scarring is common, resulting in a much lower success rate of trabeculectomy or a higher reoperation rate, use of an antifibrotic agent on a routine basis is justified. In the Philippines, the most common concentrations of MMC used are 0.2 mg/ml and 0.4 mg/ml, with exposure time varying from 2 to 5 minutes.

There are two factors to consider when using antifibrotic agents in glaucoma filtration surgery: the concentration of the agent and the duration of application. The strength of MMC application can be varied by either increasing the concentration, usually 0.4 mg/ml over 0.2 mg/ml, or increasing the duration of application to as long as 5 minutes. The total dose of the application can be calculated as concentration multiply by duration of exposure. In this study, we opted for keeping the total dose similar (0.4 mg/ml x 2 minutes versus 0.2 mg/ml x 4 minutes) in order to predict the factors affecting IOP control postoperatively with minimal effect of confounding factors. We compared a high MMC (0.4 mg/ml) concentration applied for a shorter duration (2 minutes) to a lower MMC (0.2 mg/ml) concentration applied for a longer duration (4 minutes) to prevent serious postoperative complications such as scleral necrosis, which has been reported when higher doses were used.

Several investigators studied the effects of Mitomycin-C by either using a constant concentration with varying exposure time,[8, 14] a constant exposure time but varying MMC concentrations,[6, 7, 9] or variable concentrations and exposure time.[4, 11] These studies showed no significant difference in the success of IOP control between the various MMC concentrations (0.2 mg/ml to 0.5 mg/ml), except for those with very low concentrations of 0.02 mg/ml[6] to 0.1 mg/ml[7] where the success rate was significantly lower. Varying the exposure time (2 to 5 minutes) also did not show any significant difference among the different groups. Our study similarly showed no significant difference in IOP lowering between the two groups studied at an average follow-up of 20 weeks (Table 3). The survival curves of the two treatment groups were also similar (Figure 1). However, there is a possibility that had the observation period been prolonged, there may result a significant difference between the two, especially for the period beyond 35 weeks.

The incidence of complications in this study was similar between the two treatment groups. Several studies reported a higher incidence of postoperative hypotony[7] and hypotony maculopathy[6, 8] in those treated with higher concentrations of MMC and longer duration of exposure. Other studies[9, 11] reported no significant difference. Our study had only 3 cases of hypotony, 2 of which occurred in the 0.2 mg/ml concentration. The similarity of the total dose in the 2 treatment groups in this study may account for the no difference in the incidence of hypotony. Had the duration of exposure been varied, such as to 4 or 5 minutes for the higher concentration MMC especially in the low-risk group, the occurrence of hypotony may increase dramatically.

The univariate analysis (Table 4) of the predictive factors for postoperative IOP showed that preoperative IOP and the type of filtering bleb were the only significant predictors. Patient factors such as age and gender were not predictors indicating that MMC use during glaucoma filtration surgery is independent of the patient. Angle status or the type of glaucoma (high risk versus low risk of surgical failure) was not predictive, indicating that MMC use is independent of glaucoma type. The concentration of MMC and the duration of application were also not predictors in this study. Since the total dose of the two treatment groups was similar, the effect of MMC concentration and duration of application may have been negated. Varying the total dose as in varying the exposure time of the higher concentration MMC may have different effects on the postoperative IOP.

In the multivariate analysis (Table 5), preoperative IOP still remained a predictor of postoperative IOP. The level of preoperative IOP had an effect on postoperative IOP or success of the filtering surgery; the higher the preoperative IOP, the greater likelihood that the filter will not fail. This is because of the definition of success rate used in this study. A higher preoperative IOP would result in a higher chance of attaining a 30% reduction of IOP. In the Cox model, for every 1 mm Hg IOP rise at baseline, there was a corresponding 0.960 or 1 mm Hg reduction in IOP during the postoperative follow-up.

In the type of filtering bleb, only diffuse and cystic blebs remained predictive in the Cox model. The more cystic the bleb (also true for diffuse), the lower the postoperative IOP. This was further supported by the mean IOP change for each type of bleb. Most of the blebs in this study were cystic (61%) with the lowest mean IOP change of 22.5 mm Hg, followed by diffuse bleb (Table 6). The vascular bleb, even though it had a large mean IOP change postoperatively, was no longer predictive of a successful filter. This could be due to the shorter follow-up (ranging from 4 to 12 weeks) occurring mostly in those with a vascular bleb. In the Cox model, an eye with a diffuse bleb has 7 times less chance of failure than a flat bleb. Eyes with vascular or cystic blebs have 1.73 and 24.4 chances of increase in probability of success, respectively, compared with a flat bleb (Table 5). Furthermore, the model showed that for every 10 mm Hg reduction from preoperative IOP, the chance of success is increased by 3.35 times ($p = 0.02$).

The regression model has an R^2 of 82%, indicating that the variability of the IOP after filtering surgery could be explained by the identified independent variables included in the model 82% of the time. Other factors, not taken into consideration in this study that may explain the other 18% of the variability are varying exposure time of the MMC concentration, varying follow-up periods, and different surgeons performing the surgery. These factors may affect the ultimate outcome in the differences between using 0.4 mg/ml over 0.2 mg/ml of MMC. Future studies should address these issues, preferably the same surgeon and the same but longer follow-up period for all patients and varying the exposure time.

In summary, there is no significant difference observed in the outcomes of trabeculectomies using a 0.4 mg/ml of MMC at 2 minutes versus 0.2 mg/ml of MMC at 4 minutes over an average follow-up period of 20 weeks. Preoperative IOP and type of filtering bleb are factors predictive of a successful filtration surgery.

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