A Long-term Dose-Response Study of Mitomycin in Glaucoma Filtration Surgery

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Objective: To establish the long-term, dose-response relationship between the concentration of and duration of exposure to mitomycin to a decrease in intraocular pressure (IOP) and fewer complications.

Methods: We performed a prospective double-masked, placebo-controlled, 1-year study evaluating the decrease in IOP and fewer complications of fornix-based trabeculectomy surgery in 300 eyes equally divided among therapy with placebo; mitomycin, 0.2 mg/mL, applied for 2 minutes; mitomycin, 0.2 mg/mL, applied for 4 minutes; or mitomycin, 0.4 mg/mL, applied for 2 minutes. All of the eyes had vertical and horizontal cup-disc ratios greater than 0.7.

Results: We observed significant treatment-related differences in IOP, with a decrease in IOP in all 3 mitomycin-treated groups for all of the times beyond 1 month. The number of eyes achieving strict IOP control and the development of cataract suggest a possible dose-response effect for concentration and time of exposure. Progressive lens opacification was the most frequent complication in 34 eyes (18.1%). The incidence of progressive lens changes markedly increased in subjects receiving 4 minutes of mitomycin therapy. Cataract formation was unrelated to IOP. Other complications were rare. Macular folds developed in 6 patients, with visual acuity returning to better than 20/40 in all but 1 patient.

Conclusions: A possible dose-response relationship seemed to exist between the concentration of and duration of exposure to mitomycin. Length of exposure seems to be more important than concentration. The benefits of additional decreases in IOP must be weighed against the potential for increases in the risk of complications.

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ANTIPROLIFERATIVE agents have altered our approach to glaucoma filtration surgery. Placebo-controlled studies have conclusively proved that treatment with fluorouracil significantly increases the success of filtration surgery.1-5 First described more than a decade ago,6,8 mitomycin (Kyowa Hakko Pharmaceutical, Japan) has continuously become more popular as an adjunct to filtration surgery. In part, this may be owing to its ease of application and patient acceptance compared with fluorouracil treatment. In some relatively short-term studies involving limited numbers of patients, the ability of mitomycin to lower intraocular pressure (IOP) has been found superior to fluorouracil treatment.9-13 Because of the success of antiproliferative agents in high-risk eyes, some surgeons now use them in eyes without prior intraocular surgery.16-23 The appropriate role of mitomycin is uncertain because of complications.20,23-33 Some short-term studies with a limited number of patients16,27,33 have suggested that the concentration of and duration of exposure to mitomycin may decrease IOP and cause fewer complications. To our knowledge, no long-term, placebo-controlled studies exist that evaluate a dose-response of the concentration of mitomycin and its duration of exposure on the globe. We performed such a study and report our results herein.

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RESULTS

The treatment groups were similar for age, sex, history of argon laser trabeculoplasty, use of glaucoma medications, and visual acuity at baseline (Table 1). The average degree of baseline visual field loss was moderately severe, with an overall
SUBJECTS AND METHODS

The Aravind Eye Hospital is a large, modern, urban institution in the Tamil Nadu state of southern India. All of the patients were older than 21 years, had phakic eyes, and had no prior intraocular surgery. We excluded subjects from this study if they had a history of chronic uveitis, neovascular glaucoma, or best-corrected visual acuity less than 10/200 in the eye undergoing surgery. All of the patients initially received IOP-lowering medications and had IOPs that were considered too high for their optic nerve damage. Institutional approval of the study was received and informed consent was obtained from each subject. Only the first operated on eye, per subject, was enrolled in our study.

We randomized patients into 4 treatment groups in a prospective double-masked fashion. The study medications were given to the surgeon (R.R.) by the operating room technician after the conjunctival dissection. Each eye received 2 consecutive cellulose sponges soaked with the study medication, each applied for a total of 2 minutes. Study medications were, therefore, applied for a total of 4 minutes. The treatment groups were as follows: group 1, placebo-placebo (placebo); group 2, placebo-mitomycin (0.2 mg/mL applied for 2 minutes); group 3, mitomycin-mitomycin (0.2 mg/mL applied for 4 minutes); or group 4, placebo-mitomycin (0.4 mg/mL applied for 2 minutes). The study began in May 1991.

Prior to surgery, we recorded the following data: age, sex, Snellen visual acuity, IOP at the last 3 visits to the glaucoma clinic, history of laser trabeculoplasty, and number and type of glaucoma medications. All of the patients also had perimetry performed using the Humphrey perimeter (C-24-2 or C-10-2, Humphrey Instruments, San Leandro, Calif). We prospectively noted any untoward events or complications during surgery. All of the patients were routinely admitted to the hospital for the first 5 postoperative days and were evaluated at discharge (postoperative day 5). Follow-up was continued at 1 month, 3 months, and quarterly thereafter. We analyzed the following features at each postoperative visit: best-corrected visual acuity, IOP, anterior chamber depth, bleb appearance, anterior chamber reaction, lens appearance, complications, and number of glaucoma medications required for IOP control. Intraocular pressure was measured by application. Only 1 physician (R.K.), masked to the treatment group, performed all of the measurements including the evaluation of cataracts.

One senior surgeon (R.R.) performed filtering surgery with a fornix-based flap. A cellulose sponge containing either mitomycin, 0.2 mg/mL or 0.4 mg/mL, or placebo was applied to the eye (between the sclera and conjunctiva) for 2 minutes. After the application of a second sponge, the conjunctiva was copiously irrigated with at least 60 mL of lactated Ringers solution. A lamellar scleral flap, ie, a 4-mm equilateral triangle, was outlined in the superior nasal quadrant. The flap was undermined and advanced into clear cornea. After entering the anterior chamber, a Kelley Descemet membrane punch (Storz Instruments, St Louis, Mo) excised trabecular, corneal, or scleral tissue. The surgeon performed a peripheral iridectomy. A single releasable 10-0 nylon suture was used to close the scleral flap at its apex. The conjunctival incision was closed with 2-0 polyglycin (Vicryl) wing sutures. Subconjunctival injections of gentamicin sulfate (20 mg) and dexamethasone sodium phosphate (2 mg) were given. Topical 1% atropine sulfate was instilled at the end of the surgical procedure. The releasable 10-0 nylon suture was normally removed on the fifth postoperative day if the IOP was greater than 4 mm Hg.

The postoperative regimen consisted of topical betamethasone and antibiotic gentamicin, each 4 times daily, and 1% atropine, once daily. The 1% atropine was continued at this dosage for 4 to 6 weeks and the steroid treatment (betamethasone) was tapered during 8 to 10 weeks.

Crude comparisons between treatment group baseline characteristics, postoperative IOP, and development of adverse outcomes were performed using 1-way analysis of variance for continuous variables and by the χ² test from contingency tables for categorical variables. The data were fit with a random-effects generalized least squares linear model of expected IOP over time to evaluate treatment-related differences in IOP adjusting for variation in baseline IOP, age, and length of follow-up.

Treatment-related differences in the rate of postoperative cataract progression were examined by evaluating the time to first documentation of progression. Kaplan-Meier survival analysis was used for the crude comparison of treatment groups. Multivariate analysis was performed using the Cox proportional hazards model to allow the adjustment for differences in age and the presence of preoperative cataract.
Table 1. Baseline Characteristics of Subjects by Treatment Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment Group 1 (n=71)</th>
<th>Treatment Group 2 (n=78)</th>
<th>Treatment Group 3 (n=77)</th>
<th>Treatment Group 4 (n=74)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51.5</td>
<td>51.9</td>
<td>50.2</td>
<td>53.3</td>
<td>.45</td>
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<tr>
<td>Preoperative intraocular pressure, mm Hg</td>
<td>29.1</td>
<td>28.1</td>
<td>30.6</td>
<td>30.9</td>
<td>.11</td>
</tr>
<tr>
<td>MD, dB</td>
<td>-14.8</td>
<td>-17.6</td>
<td>-16.4</td>
<td>-10.8</td>
<td>.01</td>
</tr>
<tr>
<td>CPSD, dB</td>
<td>2.5</td>
<td>3.7</td>
<td>3.3</td>
<td>2.6</td>
<td>.16</td>
</tr>
<tr>
<td>Male, %</td>
<td>32.4</td>
<td>33.3</td>
<td>32.5</td>
<td>36.5</td>
<td>.95</td>
</tr>
<tr>
<td>Prior medications, %</td>
<td>70.4</td>
<td>69.2</td>
<td>62.3</td>
<td>67.6</td>
<td>.73</td>
</tr>
<tr>
<td>Prior ALT, %</td>
<td>2.8</td>
<td>3.9</td>
<td>2.6</td>
<td>4.1</td>
<td>.95</td>
</tr>
<tr>
<td>Visual acuity &lt;20/60, %</td>
<td>23.9</td>
<td>21.8</td>
<td>24.7</td>
<td>23.0</td>
<td>.98</td>
</tr>
<tr>
<td>Cataract and visual acuity &lt;20/60, %</td>
<td>22.5</td>
<td>15.4</td>
<td>10.4</td>
<td>18.9</td>
<td>.23</td>
</tr>
</tbody>
</table>

*Means and proportions are reported for continuous and categorical variables, respectively.

†Treatment group 1 indicates placebo; 2, eyes treated with mitomycin, 0.2 mg/mL, for 2 minutes; 3, eyes treated with mitomycin, 0.2 mg/mL, for 4 minutes; and 4, eyes treated with mitomycin, 0.4 mg/mL, for 2 minutes.

‡MD indicates Humphrey mean deviation; CPSD, Humphrey corrected pattern SD; prior medications, preoperative use of topical glaucoma medications; and ALT, argon laser trabeculoplasty.

Table 2. Distribution of Glaucoma Subtype by Treatment Group

<table>
<thead>
<tr>
<th>Glaucoma Subtype</th>
<th>Treatment Group 1 (n=71)</th>
<th>Treatment Group 2 (n=78)</th>
<th>Treatment Group 3 (n=77)</th>
<th>Treatment Group 4 (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary open-angle</td>
<td>49.3</td>
<td>46.2</td>
<td>40.3</td>
<td>36.5</td>
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<tr>
<td>Primary angle-closure</td>
<td>38.0</td>
<td>37.2</td>
<td>37.7</td>
<td>44.6</td>
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<tr>
<td>Exfoliation</td>
<td>5.6</td>
<td>9.0</td>
<td>10.4</td>
<td>13.5</td>
</tr>
<tr>
<td>Pigmentary</td>
<td>2.8</td>
<td>1.3</td>
<td>1.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Other</td>
<td>4.3</td>
<td>6.3</td>
<td>10.3</td>
<td>5.4</td>
</tr>
</tbody>
</table>

*Overall χ² for comparison of proportions, P=.81.

†Treatment group 1 indicates placebo; 2, eyes treated with mitomycin, 0.2 mg/mL, for 2 minutes; 3, eyes treated with mitomycin, 0.2 mg/mL, for 4 minutes; and 4, eyes treated with mitomycin, 0.4 mg/mL, for 2 minutes.

Figure 1. Comparison of mean intraocular pressure (IOP) by treatment group during the first year following trabeculectomy. Mean IOP was determined at each time point based on the available data, excluding those who failed to appear for a scheduled visit. The change in IOP at t=0 indicates the drop from baseline to hospital discharge.

Figure 2. Comparison of mean IOP by treatment group during the first year following trabeculectomy. Mean IOP was determined at each time point based on the available data, excluding those who failed to appear for a scheduled visit. The change in IOP at t=0 indicates the drop from baseline to hospital discharge.

variable initial IOP and number of medications used prior to surgery. No evidence of interaction was found, indicating that the magnitude of the treatment effect was not different for age, preoperative IOP, or follow-up time. Further adjustment for differences among groups in severity of baseline visual acuity loss, glaucoma subtype, prior use of glaucoma medications, or prior laser trabeculoplasty did not change these results. Six subjects (3 from group 2, 1 from group 3, and 2 from group 4) underwent cataract extraction by clear corneal incision prior to their final follow-up examination. Exclusion of observations following the second surgery for these subjects did not affect the results.

Of the 221 subjects with at least 1 year of follow-up, a larger proportion of those in the placebo group had a final IOP greater than 18 mm Hg or required medication for IOP control than in any of the mitomycin-treated groups (Table 3). The proportion of subjects experiencing a decrease in IOP of at least 25% was similar in all 4 groups. None of these observed differences were statistically significant.

A clinically obvious progressive lens opacity (a best-corrected Snellen visual acuity decrease >3 lines caused by cataract) was the most frequent complication, occurring in 54 eyes (18.1%). A crude comparison of the time to cataract progression by Kaplan-Meier analysis showed significant differences in the rate of cataract development between groups (P=.007, log-rank test) (Figure 2). The results of the Cox proportional hazards model showed a significant increase in the risk of cataract progression among subjects in group 3 after adjusting for age (Table 4). Further adjustment for the presence of cataract at baseline did not affect these results. To determine whether the increased risk of cataract progression was owing to differences in IOP, anterior chamber depth, or both, as opposed to a direct effect of drug exposure, the data were fit with another set of proportional hazards models adding IOP and anterior chamber depth (graded as <50% of normal) as time-dependent predictors. This analysis revealed that after adjusting for age and treatment group, anterior chamber depths at hospital discharge and 1 month following surgery were independently associated with cataract progression, with relative hazards of 2.37 (95% CI=1.25, 4.47) and 4.27 (95% CI=1.64, 11.2), respectively. No independent association between cataract progression and IOP was observed. After adjusting for differences in age and anterior chamber depth at hospital discharge and 1 month
following surgery, the pattern of increased risk of cataract associated with high-dose mitomycin persisted. The adjusted relative hazard for group 2 vs the control group was 1.45 (95% CI=0.57, 3.73; P=0.44), while the relative hazard for group 3 vs the control group was 3.37 (95% CI=1.40, 8.16; P=0.007) and for group 4 vs the control group was 2.09 (95% CI=0.83, 5.24; P=.12).

Complications other than cataract were rare, with most occurring prior to hospital discharge (Figure 3). Complications prior to discharge were minor, self-limited, or both and included hyphema in 8 (2.7%) of the subjects, temporary bleb leak in 18 (6.0%) of the subjects, corneal epithelial defect in 5 (1.7%) of the subjects, choroidal detachment in 13 (4.4%) of the subjects, and folds in the macula in 19 (6.4%) of the subjects. There were no differences in the rate of these complications among treatment groups.

Six subjects had macular folds that persisted beyond 1 month following surgery. All 6 of these subjects had been treated with mitomycin (2 from each mitomycin-treated group). The range of IOPs in these subjects was from 2 to 6 mm Hg. In 2 subjects, best-corrected visual acuity remained 20/20; visual acuity was worse than 20/40 in only 1 of these subjects. Three of the 6 subjects had at least 1 diopter of myopia, while only 9.2% of the remaining subjects had this degree of myopia.

Complications occurring after discharge were rare. All 3 cases of late choroidal effusion occurred in subjects in group 3. In 1 case, choroidal detachment persisted until the 6-month follow-up visit. One patient in group 2 and another in group 4 had corneal dehiscence by 6 months. There was only 1 case of late bleb leak, occurring at 12 months in a subject from group 2. No serious complications such as endophthalmitis, suprachoroidal hemorrhage, or retinal detachment occurred.

Visual acuity fluctuated during the first 2 postoperative months but seemed similar among treatment groups (Figure 4). The placebo group had the smallest and the group with the longest exposure time had the highest proportion of subjects with best-corrected visual acuity less than 20/60 at the 3-month postoperative examination and all subsequent visits. The pattern of change in postoperative visual acuity was consistent with the differing rates of cataract progression among treatment groups.

**COMMENT**

To our knowledge, this is the first prospective long-term, placebo-controlled, dose-response evaluation of mitomycin used in glaucoma filtration surgery. We observed a trend toward a dose-response effect in mitomycin concentration and exposure time that persisted throughout the duration of the study. All of the concentrations of mitomycin decreased IOP and increased success sig-
significantly more than placebo. Although not statistically significant, the higher the concentration or the longer the exposure time, the greater the IOP control in medication-free subjects. The mean difference in the decrease in IOP in some groups compared with placebo might have been only 2 mm Hg. However, this might represent an additional 15% to 20% decrease in IOP, which in some eyes could be clinically significant. Previous studies have found that the success rate of trabeculectomy without antiproliferative agents continues to diminish with time. It could be that the addition of mitomycin could enhance a longer success rate, similar to that previously seen with full-thickness filtration surgery.

It was encouraging to learn that 73% of the eyes met even the strictest definitions of successful decrease in IOP 1 year after surgery, even without the addition of an antiproliferative agent. This is especially promising considering that the mean (±SD) was −15 ± 13.8 dB and most eyes had maximal disc cupping. With the addition of an antiproliferative agent, the success rate reached 86%, but with an increased incidence of some complications, particularly cataract. One must be cognizant of this trade-off when using an antiproliferative agent and ensure that the potential gain of a decrease in IOP is worth the potential risk of an increase in cataract formation.

Cataract was the most serious surgical complication in our series. It is important to note that 6 eyes had progression of cataract serious enough to warrant surgery prior to the final follow-up visit. None of these subjects received placebo. While admittedly this is only a short period, this relationship between cataract progression and the use of mitomycin should be emphasized. We found a definite correlation between a high exposure time to mitomycin and an increased rate of cataract formation. There has been a presumptive association between cataract formation and filtration surgery in previous studies.

One-year follow-up surgery, and anterior chamber depth at hospital discharge and 1 month following surgery, we noted that longer exposure to mitomycin was associated with increased risk of cataract formation. Our results suggest that surgeons should use appropriate caution when using longer exposures of mitomycin in phakic eyes.

Cataract formation has potentially serious consequences in a developed nation as further surgery to remove cataract could increase the risk of filtration failure. This complication has even graver consequences in a developing nation in which cataract itself is the leading cause of blindness.

Persistent choroidal effusions and hypotony maculopathy are serious, potentially visually disabling, complications. Our results agree with those of others in that these complications are related to the use of antiproliferative agents, younger age of the subject, and myopia. Fortunately, 5 of 6 eyes with persistent macular folds attained visual acuity better than 20/40 without additional surgical intervention. Exposure, rather than concentration, seems to be highly correlated with an increased complication rate.

It is noteworthy that antimetabolite filtration surgery was performed with a fornix-based flap rather than a limbal-based flap. We detected no persistent wound leaks at the limbal wound margin despite the direct application of mitomycin. We have no explanation for why the mitomycin may have inhibited wound closure at the scleral flap incision but not at the conjunctival wound.

The results of our study should be interpreted with caution. Our study population was composed of only eyes from southern India, all with marked glaucoma damage. The subjects had no prior glaucoma or lens surgery. Fewer classes of IOP-lowering medications were available than in other nations. Most of the subjects never had laser trabeculoplasty. All of the surgical procedures were performed by a glaucoma specialist (R.R.). Only 2 different concentrations of and durations of exposure to mitomycin were evaluated. Our results are also inapplicable to pseudophakic or aphakic eyes. Our study was not designed to determine whether an increased preservation of visual acuity is associated with the use of mitomycin. Although we discuss a 1-year follow-up, glaucoma is a chronic disease. A longer follow-up would be helpful to determine the stability of visual acuity function. Our results suggest that using appropriate concentrations of and exposure times to mitomycin can enhance the ability of trabeculectomy to lower IOP with minimal additional complications.
REFERENCES