Comparison of Low-Dose Intraoperative Mitomycin-C vs 5-Fluorouracil in Primary Glaucoma Surgery: A Pilot Study

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BACKGROUND AND OBJECTIVE: This study was undertaken to compare the efficacy and safety of low-dose intraoperative application of mitomycin-C (MMC) with that of 5-fluorouracil (5-FU) in primary trabeculectomy.

PATIENTS AND METHODS: A non-randomized prospective study was performed between August 1994 and November 1995. Thirty-two eyes of 16 consecutive patients who underwent trabeculectomy for uncontrolled glaucoma of various causes form the study group. The mean age was 46.8 ± 9.9 years. The first eye received MMC (0.2, 0.4 mg/ml), fellow eye received 5-FU (50 mg/ml), for 1 minute intraoperatively. Bleb characteristics and intraocular pressure (IOP) control were analyzed. Success of surgery based on IOP control was measured by 3 different criteria: IOP less than 21 mm Hg; IOP less than 21 mm Hg with more than 30% reduction; and IOP less than 16 mm Hg with more than 30% reduction.

RESULTS: Mean preoperative IOP was 31.4 ± 12.7 mm Hg in MMC group and 27.8 ± 8.8 mm Hg in 5-FU group. Mean follow-up in MMC group was 16.12 ± 8.17 months; in 5-FU group 13.37 ± 8.19 months. At last follow-up all 5-FU blebs were non-ischemic, while 4 eyes in the MMC group showed non-ischemic blebs, and 12 eyes had ischemic blebs. There was no statistically significant difference between MMC group and 5-FU group success rates with all 3 criteria. Success rates were: IOP less than 21 mm Hg: 100% in both groups; IOP less than 21 mm Hg with more than 30% reduction: MMC group 93.8%, 5-FU group 75%; less than 16 mm Hg with more than 30% reduction: MMC group 87.5%, 5-FU group 68.8%.

CONCLUSIONS: Low-dose intraoperative MMC and 5-FU can provide control of IOP in primary trabeculectomy, 5-FU group showed more non-ischemic blebs.


INTRODUCTION

The most common cause of failure of glaucoma filtering surgery is episcleral scarring at the filtration site. Agents that inhibit fibroblast proliferation have been shown to increase the success rate of filtering surgery. Today the most commonly used antifibrotic agents are 5-fluorouracil (5-FU) and mitomycin-C (MMC).
Table 1. Preoperative Data

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Age (in years)</th>
<th>46.81 ± 9.92</th>
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</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (56.25%)</td>
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<tr>
<td>Female</td>
<td>7 (43.75%)</td>
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<table>
<thead>
<tr>
<th>Group Characteristics</th>
<th>MMC group (n=16)</th>
<th>5-FU group (n=16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP mm Hg</td>
<td>31.4 ± 12.7</td>
<td>27.8 ± 8.8</td>
<td>0.36</td>
</tr>
<tr>
<td>Number of Medications</td>
<td>1.38 ± 0.80</td>
<td>1.63 ± 0.62</td>
<td>0.38</td>
</tr>
</tbody>
</table>

MMC=Mitomycin C
5-FU=5-fluorouracil
IOP=Intraocular pressure.

5-FU was initially used postoperatively as multiple subconjunctival injections. However repeated injections are uncomfortable, inconvenient, and can be associated with complications such as corneal epithelial defects. Studies have shown MMC to be effective in increasing the success of filtering surgery with a single intraoperative application, thus avoiding the need for postoperative injections. More recently, 5-FU has been used as a single intraoperative application in experimental and clinical studies. It has been presumed that the antifibrotic effect of antimitabolite is dose- and time-dependent. The reduction of dosage or time of exposure to antimitabolite might decrease the incidence of thin blebs and overfiltration, thus avoiding the attendant complications of wound leaks, hypotony, and choroidal detachment. This study was undertaken to compare the efficacy and safety of low-dose intraoperative application of MMC with that of 5-FU in primary trabeculectomy.

**PATIENTS AND METHODS**

Sixteen consecutive patients who underwent bilateral filtering surgery between August 1994 and November 1995 at our institution were the subjects of this study. The indication for filtering surgery was uncontrolled intraocular pressure with maximal medical therapy or advanced glaucomatous disease. Multiple recordings of the intraocular pressure were performed, but the intraocular pressure recording just before surgery was taken for study evaluation. Patients were considered to have advanced glaucomatous disease if they had only a central residual island of vision or an arcuate scotoma encroaching to within 5° of central fixation. In cases where visual fields were unreliable (as in eyes with extremely miotic pupils), or where field examination was not feasible (as in eyes with poor visual acuity), the state of the optic disc guided the definition of advanced glaucoma. Largely the glaucomatous disease was symmetrical in both eyes of all subjects.

There was no difference in preoperative antiglaucoma medication between the 2 groups. Preoperative medications consisted of topical beta blockers and miotics. The type of glaucoma treated in this series was primary open angle glaucoma (9 subjects), primary angle closure glaucoma (5 subjects), juvenile glaucoma (1 subject), and pigmentary glaucoma (1 subject). None of the eyes in this study had undergone prior ocular surgery. Preoperative examination included best corrected Snellen's visual acuity, slit lamp biomicroscopy, applanation tonometry, gonioscopy and optic disc evaluation using a 90 diopter (D) lens. Visual field examination was performed. Informed consent was obtained in all patients.

The first eye received intraoperative MMC for 1 minute while the second eye received intraoperative 5-FU for 1 minute. A dose of 0.4 mg/ml of MMC was used in 13 eyes. In 3 eyes with myopia greater than 5.00 D, 0.2 mg/ml of MMC was used. A dose of 50 mg/ml of 5-FU was used in 16 eyes. Trabeculectomy was performed in all eyes by a single surgeon. A limbus based conjunctival flap was raised in the superior nasal quadrant 8 to 10 mm from the limbus. A 3 × 2 mm cellulose sponge soaked in the appropriate antimitabolite was placed in contact with the exposed episcleral tissue with conjunctival flap draped over it for 1 minute.

Following removal of the cellulose sponge, the tissues were gently rinsed with ringer lactate solution. A
Table 2. Change in IOP Following Removal of the Releasable Suture

<table>
<thead>
<tr>
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<th>MMC group (n = 7)</th>
<th>5-FU group (n = 9)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Pre-release IOP</td>
<td>31.6 ± 10.0</td>
<td>21.2 ± 2.8</td>
<td>0.03</td>
</tr>
<tr>
<td>(range 18-44)</td>
<td></td>
<td>(range 18-25)</td>
<td></td>
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<tr>
<td>Post-release IOP</td>
<td>15.7 ± 6.0</td>
<td>12.3 ± 3.2</td>
<td>0.21</td>
</tr>
<tr>
<td>(range 10-25)</td>
<td></td>
<td>(range 0-18)</td>
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A triangular partial thickness scleral flap was dissected, corneoscleral block of tissue was excised, and a peripheral iridectomy was performed. The scleral flap was tightly apposed with 1 releasable suture at the apex and 2 interrupted sutures close to the base of the triangle using 10-0 monofilament nylon. The anterior chamber was formed with ringer lactate solution. The conjunctiva and Tenon's capsule were sutured in separate layers using 8-0 polyglactin on a spoolated needle.

At the conclusion of surgery 0.5 ml (2 mg) dexamethasone was injected subconjunctively into the inferior fornix. The eye was patched after instilling atropine (1%) and betamethasone (0.1%) eye drops. Postoperatively, all patients received topical atropine (1%) eye drops, twice a day for 2 weeks, and betamethasone (0.1%) eye drops, 4 times a day for 6 weeks. The releasable suture was released within the first postoperative week if the intraocular pressure was more than 18 mm Hg. In cases not requiring release of the releasable suture, the suture was trimmed close to the limbus allowing its retraction into the scleral flap. Postoperative complications, if any, were recorded.

We have identified 2 relatively distinct types of blebs; ischemic and non-ischemic. The ischemic variety is characterized by presence of an absolutely pale bleb with a clear, well-defined demarcation line from remaining normal conjunctiva which facilitated enhanced visibility of the underlying scleral flap and sutures. In contrast, the second variety, which we labeled non-ischemic, is characterized by a bleb where- in the vessels from the surrounding conjunctiva merged diffusely with bleb area without a clear demarcation line. In this situation the scleral flap and sutures were not easily visualized. Success was determined by three different criteria. A final IOP of less than 21 mm Hg; a final IOP less than 21 mm Hg with more than 30% reduction in IOP; and a final IOP less than 16 mm Hg with more than 30% reduction in IOP.

Hypotony was defined as IOP less than or equal to 5 mm Hg at 3 months. Continuous variables were analysed using the Student's t-test, while categorical data was analyzed using the chi-squared test (Yates corrected) and the Fischer's exact test. A P value of < 0.05 was considered significant.

RESULTS

Of the 16 patients, 9 were males, and 7 were females with a mean age of 46.81 ± 9.92 years. Preoperative data is shown in Table 1. There were no statistically significant differences in these baseline variables. Change in IOP following removal of releasable suture is shown in Table 2. Although the pre-release IOP was significantly higher in the MMC group (P = 0.033),

Table 3. Mean Intraocular Pressures at All Time Intervals

<table>
<thead>
<tr>
<th></th>
<th>MMC Group IOP (mm Hg)</th>
<th>5-FU group IOP (mm Hg)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>31.4 ± 12.7</td>
<td>27.8 ± 8.8</td>
<td>0.36</td>
</tr>
<tr>
<td>3 months</td>
<td>9.50 ± 4.1</td>
<td>10.1 ± 3.3</td>
<td>0.67</td>
</tr>
<tr>
<td>6 months</td>
<td>8.8 ± 3.1</td>
<td>11.0 ± 3.1</td>
<td>0.12</td>
</tr>
<tr>
<td>Last follow-up</td>
<td>11.1 ± 4.0</td>
<td>12.5 ± 3.7</td>
<td>0.44</td>
</tr>
</tbody>
</table>

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the post-release IOP was similar in both groups. Mean follow-up in the MMC group was 16.12 ± 8.17 months (range 6-30 months), and in the 5-FU group was 13.37 ± 8.19 months (range 3-24 months). The mean IOP in the 2 groups at all time intervals was not statistically different (Table 3). Table 4 lists the success rates for trabeculectomy according to the 3 different success criteria. These results are based on the IOP at the most recent visit regardless of the length of follow-up. The Kaplan-Meier survival curve is shown in Figure 1. Survival varies according to the criteria used to define success. None of the eyes in each group needed any additional medication for control of IOP during the follow-up. There was no statistically significant difference between the MMC group and the 5-FU group success rates with all 3 criteria.

Non-ischemic blebs (Figure 2) were noted in 16 eyes (100%) in the 5-FU group and in only 4 eyes (25%) in the MMC group ($P < 0.01$). Ischemic blebs (Figure 3) were seen in 12 eyes (75%) in the MMC group and none in 5-FU group ($P < 0.01$). Pre- and postoperative visual acuities are depicted in Figure 4. At last follow-up, 2 eyes (12.5%) in the MMC group and 3 eyes (18.75%) in the 5-FU group showed loss of visual acuity by 2 or more lines. Cataract progression was the only cause for loss of visual acuity in all patients. One eye (6.3%) in the 5-FU group showed improvement in visual acuity due to clearing of corneal edema.

The postoperative complications are shown in Table 5. In the early postoperative period, a shallow anterior chamber was noted in 3 eyes (18.8%) of the MMC group, as compared to 2 eyes (12.5%) in the 5-FU group ($P = 0.15$). Hyphema occurred in 2 eyes (12.5%) in the MMC group and in none of the eyes in the 5-FU group ($P = 0.07$). These complications resolved without surgical intervention. Hypotony was noted at 3 months follow-up in 3 eyes (18.8%) of the MMC group, and in 2 eyes (12.5%) of the 5-FU group ($P = 0.15$). However, wound leaks and hypotony mac-
ulopathy were not noted in this series. The IOP increased in 4 eyes by 12-15 months. However, in one eye in MMC group, intraocular pressure remained at 5 mm Hg at 21 months follow-up.

**DISCUSSION**

Use of antimetabolites along with filtration surgery has become an established practice in relevant clinical situations. The most commonly used antimetabolites are MMC and 5-FU. To the best of our knowledge there is no study that compares the use of low-dose intraoperative MMC and 5-FU. As elucidated already, we used 3 criteria to analyze the success based on IOP. Both groups achieved final IOP of less than 21 mm Hg. Final IOP of 21 mm Hg may not be indicative of stabilized glaucoma. Hence, 2 more success criteria were included to define the success or failure. This provided a more accurate indication of whether the results we were aiming for in our patients were being achieved. According to our second criterion (IOP less than 21 mm Hg with more than a 30% drop in IOP), 93.8% (15/16) in MMC group, and 75% (12/16) in 5-FU group, achieved success. Ac-

<table>
<thead>
<tr>
<th>Success criteria</th>
<th>MMC group eyes(%)</th>
<th>5-FU group eyes(%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP &lt; 21 mm Hg</td>
<td>16 (100)</td>
<td>16 (100)</td>
<td>1.00</td>
</tr>
<tr>
<td>IOP &lt; 21 mm Hg and &gt; 30% drop in IOP</td>
<td>15 (93.8)</td>
<td>12 (75.0)</td>
<td>0.33</td>
</tr>
<tr>
<td>IOP &lt; 16 mm Hg and &gt; 30% drop in IOP</td>
<td>14 (87.5)</td>
<td>11 (68.8)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

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<table>
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<tr>
<th>Table 5. Postoperative Complications</th>
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<tbody>
<tr>
<td>MMC group (n=16)</td>
</tr>
<tr>
<td>Shallow anterior chamber</td>
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<tr>
<td>Hyphema</td>
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</tbody>
</table>

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According to our third criterion (IOP less than 16 mm Hg with a more than 30% drop in IOP), 87.5% (14/16) in MMC group, and 68.8% (11/16) in 5-FU group, achieved success. With these 2 criteria, although success rates were higher in the MMC group compared to the 5-FU group, this difference was not found to be statistically significant. The small sample size has diminished our ability to detect significant differences between the 2 groups.

Khaw et al.9 in an in vivo rabbit model of glaucoma filtration surgery, showed that use of intraoperative 5-FU of 50 mg/ml significantly prolonged the survival of filtration blebs. But compared to MMC, the effect was less marked and the blebs were thicker. In our series, the difference in bleb appearance between the 2 groups could be explained by the different mechanism of action of the 2 drugs. Mitomycin-C acts on all the phases of fibroblast cell cycle,9 has an antiangiogenic effect,17 and produces thinner and more avascular blebs. 5-Fluorouracil, which is cell cycle specific,9 is likely to produce thicker, more diffuse, and less avascular blebs. The major side effect observed following usage of MMC in eyes undergoing primary trabeculectomy was hypotony with or without maculopathy.15,18-20

Zacharia et al.20 reported a 37.2% incidence of ocular hypotony following primary trabeculectomy with MMC. They also observed that hypotony occurs more frequently in eyes with longer duration of application. In our MMC group, only 1 eye had hypotony at last follow-up, and there was no case of hypotony maculopathy. The reduction of concentration and exposure time of MMC in our series possibly contributed to the relative lack of hypotony, and for the absence of hypotony maculopathy. The present study suggests that in primary trabeculectomy, intraoperative 5-FU (50 mg/ml for 1 minute application) is probably as effective as intraoperative MMC (0.2–0.4 mg/ml for 1 minute application) and avoids the problem of multiple postoperative 5-FU injections. Both seem to have reduced the IOP to safe levels without medications. Reduced concentration and exposure time of MMC has decreased the incidence of prolonged hypotony and its sequelae.

The bleb characteristics appeared to be different; 5-FU blebs were non-ischemic, and MMC blebs were mostly ischemic. Since bleb-related endophthalmitis tends to occur commonly with thin blebs,21,22 it remains to be seen whether 5-FU blebs are safer. The advantage of the present study was that eyes were assessed, rather than patients, so as to counter the inherent variability in fibrosis from patient to patient. Since the same patient received both MMC and 5-FU, the comparison of the 2 drugs could be more appropriate. The limitations of the study are the lack of randomization and masking, the small numbers, and the intermediate follow-up. Further investigations are needed in a much larger series. Long-term follow-up is also needed to specifically look for prolonged IOP control and other late complications.

REFERENCES

11. Lanigan LP, Stuermer J, Baez KA, Hitchings RA, Khaw PT. Single intraoperative applications of 5-fluorouracil

INTRAOPERATIVE MMC VS. 5-FU - Vijaya et al.


