Episceral Versus Combined Episceral and Intracocular Application of Mitomycin-C in Trabeculectomy

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■ BACKGROUND AND OBJECTIVE: To determine whether intracocular exposure to mitomycin-C (MMC) improves the control of intraocular pressure (IOP), increases the incidence of complications, or both.

■ PATIENTS AND METHODS: The authors retrospectively evaluated 38 eyes of 29 patients following the intraocular application of MMC (0.2 mg/ml; 5 minutes). In 21 eyes the MMC-soaked sponge was applied to the intact episclera (episceral group). In 17 eyes, two sponges, one episcleral and the other intracocular (sandwich group), were applied. The median follow-up times were 19.0 (episceral group) and 24.0 (sandwich group) months. Outcome measures were the IOP, the number of medications, success rates, and the incidence of complications.

■ RESULTS: The only statistically significant difference between the two groups was the 2-week postoperative IOP, which was significantly lower in the episcleral group (P = .0314).

■ CONCLUSION: Because there is no additional benefit, the authors recommend that the intracocular application of MMC be avoided. However, they did not observe increased complication rates when MMC was applied in this way.


INTRODUCTION

The intraocular application of mitomycin-C (MMC) increases the success rate of trabeculectomy and reduces the mean postoperative intraocular pressure (IOP). Despite its effectiveness, there is some concern about the side effects of MMC. The optimal mode of application has not been established.

A recently published study compared intracocular application of MMC with combined episcleral and conjunctival or Tenon’s layer application of MMC. No statistically significant difference was found between the two groups regarding IOP or number of medications. However, fewer postoperative medications were needed in the episcleral group.

Our study retrospectively compares two groups of patients with different sites of MMC application: episcleral versus combined intracocular and episcleral. Contact of the sponge with the conjunctiva or Tenon’s layer was avoided in both groups. We wanted to determine whether intracocular exposure to MMC improves the control of IOP, increases the incidence of complications, or both.

PATIENTS AND METHODS

We retrospectively reviewed the records of 41 consecutive eyes that had primary trabeculectomies with
adjunctive use of MMC from May 1994 through February 1995. Within this period, two different surgical techniques were used: the episcleral technique and the sandwich technique. Patients were assigned by chance to one of the two techniques without any selection criteria. Three patients were lost to follow-up within 1 year postoperatively and were not included in the evaluation. A total of 38 eyes of 29 patients were included in the study. Twenty-one eyes were assigned to the episcleral group and 17 to the sandwich group (Table 1).

The surgical approach was the same in both groups, with the site of MMC application being the only difference. A limbus-based conjunctival flap was formed in all of the eyes. This was followed by episcleral cauterization. In the episcleral group, we exposed the intact episclera to half of an MMC-soaked sponge (Cornea Light Shield, Merocel Corp., Mystic, CT) prior to the preparation of the scleral flap. In the sandwich group, we first prepared the lamellar scleral flap and then applied two MMC-soaked sponges, one to the bottom of the scleral bed and the other on top of the scleral flap. Both sponges were trimmed to the size of the scleral flap. In both groups, conjunctival or Tenon's layer contact with the MMC-soaked sponge was strictly avoided by elevating the conjunctiva at four points. The MMC concentration was 0.2 mg/ml and the application time was 5 minutes in both groups. Also in both groups, the MMC application was followed by thorough irrigation. The scleral flap was trapezoidal, with a size of $3 \times 4 \times 5$ mm. In all of the eyes, surgery was completed with trabeculectomy, iridectomy, readaptation of the scleral flap with two 10-0 nylon sutures, and closure of the Tenon's layer and conjunctiva with a running 7-0 polyglactin and 6-0 cargut suture.

The indications for adjunctive MMC application were primary open-angle glaucoma or pseudoexfoliation glaucoma with severely damaged visual fields, juvenile glaucoma, noncompliance with or poor tolerance of topical therapy, and increased risk of surgical failure (previous failure of the other eye, previous continuous-wave YAG laser, or chronic polyarthritis) (Table 2). Eyes that had previously failed filtering surgery were excluded from this study.

During the first week postoperatively, IOP was measured and possible complications were carefully registered daily. Thereafter, uncomplicated cases were observed at 1- to 2-week intervals during the first month postoperatively; complicated cases were observed more frequently. After the first month postoperatively, follow-up intervals were, in most cases, every 1 to 3 months for the first year. Thereafter, we called the patients twice: between months 13 and 18 and, if possible, between months 19 and 24.

Regarding IOP values, the preoperative value was defined as the peak IOP with maximum tolerable therapy. Postoperatively, we evaluated the IOP at 1 week and 2 weeks (single measurement), 4 to 8 weeks, 2 to 3 months, 4 to 6 months, 7 to 12 months, 13 to 18 months, and 19 to 24 months (maximum IOP value where possible). Additionally, we evaluated the early postoperative minimum IOP and the IOP on the last day of follow-up. For each IOP measurement, the corresponding antiglaucomatous medication was quantified as a therapeutic index (Table 3).
During each follow-up visit a slit-lamp examination was performed, with possible complications and the appearance of a filtering bleb being of special interest. Visual acuity and visual fields were evaluated preoperatively and 6 to 18 months postoperatively. In some cases an old automatic perimeter, which is no longer available for follow-up visits, was used. The visual fields of 31 eyes were observed. Secondary interventions and reoperations were evaluated.

Success was defined as follows: full success (SF < 21) was an IOP below 21 mm Hg without antiglaucomatous therapy, a pressure reduction of 20% or more, and no serious complications; qualified success (SQ < 21) was an IOP below 21 mm Hg and a pressure reduction of 20% or more regardless of antiglaucomatous therapy; and failure (F < 21) was an IOP of 21 mm Hg or more and a pressure reduction of 20% or less despite maximal antiglaucomatous medication. Additionally, we defined similar success criteria with the target pressure of less than 17 mm Hg (SF < 17, SQ < 17, and F < 17). The following complications were regarded as serious: endophthalmitis, bleb infection, hypotonous maculopathy, and visual field center loss.

We used Student’s t tests for the statistical comparison of IOP differences between the groups. Categoric data such as complication rates were compared by means of chi-square tests. Differences appearing with P values of less than .05 were considered statistically significant.

RESULTS

Figure 1 shows the mean IOP values of the two groups during the follow-up period. The mean IOP of both groups was below 10 mm Hg 1 week postoperatively and remained between 11 and 14 mm Hg after the first postoperative month. During the 19- to 24-month time frame, the mean IOP was 12.9 mm Hg in the episcleral group and 15.4 mm Hg in the sandwich group. The Student’s t test revealed a significant difference only at 2 weeks postoperatively, with the sandwich group showing the higher mean IOP level \( P = .0314 \). The mean minimum IOP was not statistically significantly different between the groups. It was 5.3 mm Hg (± 4.5) for the episcleral group and 3.7 mm Hg (± 3.6) for the sandwich group. The mean final IOP was 13.1 mm Hg (± 3.6) for the episcleral group and 14.5 mm Hg (± 5.2) for the sandwich group. There was no statistically significant difference in mean final IOP between the two groups.

In both groups, the therapeutic index dropped from more than 3 preoperatively to values near 0 postoperatively and then slowly increased to a final value of 0.27 in the episcleral group and 0.42 in the sandwich group (Fig. 2). At no time was there a significant difference in the therapeutic index between the two groups using the Student’s t test. Figure 3 presents a scattergram of IOP over time for both groups. One week postoperatively there were several hypotonous eyes, but only a few of them remained hypotonous for months. At 4 weeks postoperatively and thereafter, most of the eyes had IOPs between 10 and 17 mm Hg.

The percentages of eyes with full success, qualified success, and failure are presented in Figure 4 for both groups combined. There was a slight decrease in the percentage of full success, from 97% (32 of 33 eyes) 2 weeks postoperatively to 61% (20 of 31) in the second
Figure 2. Mean therapeutic indices of the two groups throughout the follow-up period. The solid rectangles indicate the episcleral group. The open rectangles indicate the sandwich group.

Figure 3. Scattergram of the intraocular pressure values of all patients throughout the follow-up period.

Figure 4. Cumulative percentages of full success, qualified success, and failure of all patients throughout the follow-up period, using a target pressure of 21 mm Hg.

Figure 5. Cumulative percentages of full success, qualified success, and failure of all patients throughout the follow-up period, using a target pressure of 17 mm Hg.

postoperative year. The percentage of qualified success remained stable, between 100% and 92% (22 of 24) throughout the follow-up period.

Figure 5 shows the percentages of eyes with full success, qualified success, and failure when the pressure criterion was 17 mm Hg (instead of 21 mm Hg). The percentage of full success decreased from 88% (29 of 33 eyes) 2 weeks after surgery to 56% (15 of 25) in the 7- to 12-month time frame. Thereafter, it remained stable. The percentage of qualified success remained stable, between 90% (30 of 33) and 75% (22 of 29) throughout the follow-up period. Chi-square tests failed to reveal any significant differences in these percentages between the groups.

At the end of the follow-up period, the success percentages for the two groups combined were 68% for SF < 21 (26 of 38 eyes), 95% for SQ < 21 (36 of 38), 5% for F < 21 (2 of 38), 58% for SF < 17 (24 of 38), 79% for SQ < 17 (30 of 38), and 21% for F < 17 (8 of 38). Chi-square tests failed to reveal significant differences in these percentages between the groups for both IOP criteria ($P = .23$ and $P = .42$, respectively).

Table 4 summarizes the early postoperative complications of both groups. The most frequent complications were hypotony (24 of 38 eyes) and associated problems (choroidal detachment and iridocorneal touch). These three problems mostly disappeared without intervention within a maximum of 2 weeks. Four eyes needed early postoperative intervention—viscoelastic injections in 2 (episcleral group) and secondary suturing because of bleb leakage in 2 (sandwich group). Three of 24 hypotonous eyes had prolonged hypotony, 1 of them with 6-week choroidal detachment (despite 3 viscoelastic injections).

The most frequent late postoperative complication was the development of cataract or the progression of preexisting cataract (Table 5). The most serious late postoperative complication was persistent hypotony in 3 eyes, 2 of which had a macular pucker. The final visual acuities of these 2 eyes were 6/8 and
Table 4

Early Postoperative Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Group</th>
<th>Episceral</th>
<th>Sandwich</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotony ($\leq 5$ mm Hg)</td>
<td>12/21*</td>
<td>12/17</td>
<td></td>
</tr>
<tr>
<td>Choroidal detachment</td>
<td>8/21</td>
<td>7/17</td>
<td></td>
</tr>
<tr>
<td>Central iridocorneal touch</td>
<td>3/21</td>
<td>3/17</td>
<td></td>
</tr>
<tr>
<td>Peripheral iridocorneal touch</td>
<td>5/21</td>
<td>6/17</td>
<td></td>
</tr>
<tr>
<td>Hyphema</td>
<td>9/21</td>
<td>4/17</td>
<td></td>
</tr>
<tr>
<td>Wound leak</td>
<td>3/21</td>
<td>5/17</td>
<td></td>
</tr>
<tr>
<td>Fibrin</td>
<td>1/21</td>
<td>3/17</td>
<td></td>
</tr>
</tbody>
</table>

*Number/total number of eyes.

Table 5

Late Postoperative Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Group</th>
<th>Episceral</th>
<th>Sandwich</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract</td>
<td>4/19*</td>
<td>6/16</td>
<td></td>
</tr>
<tr>
<td>Persistent hypotony</td>
<td>1/21</td>
<td>2/17</td>
<td></td>
</tr>
<tr>
<td>Hypotonous maculopathy</td>
<td>1/21</td>
<td>1/17</td>
<td></td>
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</table>

*Number/total number of eyes.

Table 6

Incidence of Cataract Progression

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central iridocorneal touch</td>
<td>4/6$^*$$^\dagger$</td>
</tr>
<tr>
<td>No central iridocorneal touch</td>
<td>6/29</td>
</tr>
<tr>
<td>Choroidal detachment</td>
<td>5/15</td>
</tr>
<tr>
<td>Hypotony ($\leq 5$ mm Hg)</td>
<td>7/24</td>
</tr>
<tr>
<td>Hyphema</td>
<td>3/13</td>
</tr>
<tr>
<td>Fibrin</td>
<td>1/4</td>
</tr>
</tbody>
</table>

*Number/total number of eyes.
$^\dagger$Significant impact on cataract progression ($P = .0232$).

Eleven months after surgery, 1 patient with prolonged hypotony underwent autologous blood injection in the filtering bleb. This temporarily affected the IOP (2 to 4 mm Hg before the procedure, 6 mm Hg immediately after, and 3 mm Hg 4 months after). One eye with an encapsulated filtering bleb underwent 5-fluorouracil needling revision of the filtering bleb 23 months postoperatively. This reduced the IOP from 24 to 11 mm Hg.

Between 6 and 18 months postoperatively, the filtering blebs were well vascularized in 5 (of 20) and 5 (of 16) eyes, avascular in 4 and 5 eyes, cystic avascular in 11 and 5 eyes, and flat in 0 and 1 eye of the episcleral group and the sandwich group, respectively. There was no statistically significant difference in filtering bleb appearance between the groups using the chi-square test ($P = .39$). With both groups combined, 69% of the eyes had avascular or cystic avascular filtering blebs.

Visual fields were stable in both groups (Table 7). No visual field center wipeout occurred in 23 eyes with endangered visual field centers. In both groups, visual acuity was stable in most eyes. Only 4 eyes lost at least 2 lines of Snellen acuity (Table 8). One eye with preexisting cataract had an improvement of 2 lines of Snellen acuity after cataract surgery.

6/18 (preoperatively 6/6 and 6/38 with cataract). There was no case of endophthalmitis, bleb infection, or postoperative visual field center loss. Chi-square tests failed to reveal any significant difference between the two groups regarding the incidences of complications. Cataract surgery was performed, without complication, in 8 of the 10 eyes with cataract progression.

Table 6 lists the incidence of cataract progression after different early postoperative complications. Four of 6 eyes with central iridocorneal touch showed cataract progression, compared with 6 of 29 eyes without central iridocorneal touch. This difference was statistically significant using the chi-square test ($P = .0232$). All other complications had no significant influence on cataract progression. All 4 eyes that required an early postoperative secondary intervention later had cataract progression and needed to undergo cataract surgery.
DISCUSSION

The episcleral and sandwich techniques yielded similar good IOP reductions and similar success and failure rates. There were no statistically significant differences between the groups regarding IOP levels (Student's t tests) and success rates (chi-square tests). The only exception was the 2-week postoperative IOPs, which were significantly lower in the episcleral group compared with the sandwich group. With both groups combined, the full success rate at the end of the follow-up period was 68%, the qualified success rate was 95% (including eyes receiving topical antiglaucomatous treatment and 2 eyes with mild hyptonous maculopathy), and the failure rate was 5%. Seventy-nine percent of all eyes had a final IOP below 17 mm Hg, regardless of medical treatment.

We did not detect any statistically significant difference between the episcleral group and the sandwich group regarding complications. The most frequent complications were a reversible early postoperative hypotony (63%) and serous choroidal detachment (39%). The most serious complication was a hyptonous maculopathy in 2 eyes (5%). These 2 eyes did not suffer a marked reduction of visual acuity. We did not observe bleb-related endophthalmitis in our patients. Our success and complication rates compare favorably with those of other groups, which have reported success rates (IOP < 21 mm Hg regardless of therapy) between 70% and 100% and complication rates of 10% to 50% for choroidal detachment, 0% to 18% for hyptonous maculopathy, and 0% to 4% for bleb-related endophthalmitis.2,4,7,13-20

Tessler et al.12 recently compared two groups of patients in which application techniques similar to ours were used. The main difference between our techniques and their techniques was that in their patients the MMC made contact with the conjunctiva and Tenon's fascia, whereas we strictly avoided such contact in both groups. Tessler et al. found no statistically significant difference between intrascleral and episcleral application regarding IOP or number of medications. However, fewer postoperative medications were needed with episcleral application. Tessler et al. discussed the possibility that a reduced exposure of the conjunctiva to MMC in their group with intrascleral application may have caused this tendency. In our study there was also a tendency toward fewer postoperative medications in the episcleral group compared with the sandwich group (with therapeutic indices of 0.27 versus 0.42). This may have been caused by a smaller exposed episcleral area in our sandwich group, where we trimmed the sponge to the size of the flap.

Our findings are not in agreement with those of Seah et al.,21 who compared subconjunctival and intrascleral application of MMC. They reported a better reduction in IOP following intrascleral application. It remains unclear whether transscleral penetration of more highly concentrated MMC (0.5 mg/ml) might have caused a ciliary body toxic effect when the MMC was applied intrasclerally.

In our study, too, an enhancement of direct transscleral penetration following intrascleral application might have caused an increased exposure of the ciliary body to MMC. However, the intrascleral exposure of MMC did not result in a higher incidence of transient or persistent hypotony or hypotony maculopathy, or in a lower IOP. This might be an argument against the clinical significance of reported ciliary body toxic effects related to MMC.22,24

In an animal model, a transient reduction of aqueous flow by 20% after episcleral application of MMC has been reported.25 Extraocular application of high-dose MMC without filtering surgery reduces IOP significantly.26 These effects may be clinically irrelevant, as the concentrations and the exposed areas have been considerably larger than usual in MMC trabeculectomies.

The filtering bleb was avascular or cystic-avascular in 75% of the eyes of the episcleral group and in 67% of the eyes of the sandwich group. Because there was no direct contact of the MMC with the conjunctiva,

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TABLE 8

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Visual Acuity</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preop-</td>
<td>Postop-</td>
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<tr>
<td></td>
<td>erative</td>
<td>erative</td>
</tr>
<tr>
<td>11</td>
<td>6/15</td>
<td>6/30</td>
</tr>
<tr>
<td>16</td>
<td>6/15</td>
<td>6/30</td>
</tr>
<tr>
<td>20</td>
<td>6/12</td>
<td>6/30</td>
</tr>
<tr>
<td>33</td>
<td>6/8</td>
<td>3/60</td>
</tr>
</tbody>
</table>

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Episceral vs Episceral and Intrascleral MMC: Vass et al. 719
tiva or Tenon's fascia, this finding indicates that postoperatively there was considerable rediffusion of MMC (which had been stored intrascerally) into the conjunctiva. Kawase et al. reported tissue concentrations after application of 0.2 mg/ml MMC. Thirty minutes after application, the conjunctival concentration was 40 µg/g and the scleral concentration was 7 µg/g in the rabbit eye. The MMC concentration in a human trabeculectomy specimen was 8 µg/g. These concentrations are within the fibroblast inhibitory range.

Both the episcleral technique and the sandwich technique yielded good results that were similar. The additional intrasceral application of MMC with the sandwich technique did not show any advantages in terms of better IOP control. However, it did not cause an increase in severe complications such as persistent hypotony or hypotony-related maculopathy.

In conclusion, we failed to find an enhancement of IOP reduction or an improvement of success rates as a result of additional intrasceral exposure to MMC in the sandwich group. On the other hand, there was no evidence of increased MMC toxicity in the sandwich group. However, due to the possibly greater exposure of the ciliary body to MMC after intrasceral application and a lack of additional advantages, we advise against the additional intrasceral application of MMC. The finding of avascular filtering blebs despite strict avoidance of MMC contact with the conjunctiva should stimulate further studies on the local ocular pharmacokinetics of MMC.

REFERENCES