Outcomes of Primary Trabeculectomy With the Use of Adjunctive Mitomycin

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Objective: To investigate the efficacy and safety of adjunctive mitomycin when used during a primary trabeculectomy within a series of 89 consecutive patients at 1 and 2 years postoperatively.

Design: A cohort study of all patients who underwent primary trabeculectomy, performed by one of us (P.F.P.), between April 1, 1991, and December 31, 1994. Patients received topical mitomycin in conjunction with a corneal safety valve incision. A trabeculectomy was considered “successful” if it resulted in an intraocular pressure (IOP) of 21 mm Hg or lower and a 30% or greater reduction in the IOP at and after 1 year of follow-up, with or without medications and without a reoperation for an elevated IOP. Survival analysis was used to calculate success rates.

Results: The 1- and 2-year success rates were 85.4% and 77.9%, respectively. The mean IOP was reduced from 26.3 to 11.3 mm Hg at 1 year (n=68) and to 11.9 mm Hg at 2 years (n=56), with 60 (88.2%) of 68 patients off medication at 1 year and 47 (83.9%) of 56 patients off medication at 2 years. Trabeculectomy success rates were significantly lower in black compared with nonblack patients (76.2% vs 87.5% at 1 year, P=0.03). Trabeculectomy failure occurred throughout the follow-up period. Endophthalmitis occurred in 2 (2.2%) of the patients, and hypotonia requiring revision occurred in 4 (4.5%) of the patients.

Conclusions: Primary trabeculectomy with the use of intraoperative mitomycin lowered the IOP by 30% or more in 78% (at 2 years) to 86% (at 1 year) of the cases and is associated with a marked reduction in the percentage of patients who require glaucoma medication. Success rates must be evaluated in light of such risks as endophthalmitis and hypotony.


Mitomycin, like 5-fluorouracil, has been shown to improve the success of trabeculectomy in eyes with a high risk of surgical failure. These antifibrotic agents result in blebs that exhibit greater filtration and somewhat greater vulnerability to leakage and infection. In high-risk cases, the visual risk-benefit ratio for using antifibrotic agents is favorable.

The risk-benefit ratio of using antifibrotic agents is less well established in primary filtering surgery. For this study, primary trabeculectomy was defined as a trabeculectomy performed in an eye not previously operated on and not deemed to be at high risk for trabeculectomy failure. From the overall study analysis were eyes with glaucoma associated with anterior segment neovascularization, uveitis, and the iridocorneal endothelial syndrome, as well as eyes with juvenile glaucoma. In favor of the use of antifibrotic agents in primary filtering surgery is the observation that surgery performed without them generally yields suboptimal results, with half of the patients requiring supplemental medical therapy within 2 years. Further, the mean intraocular pressure (IOP) 5 years after surgery is usually 16 to 21 mm Hg, and 35% to 58% of patients with glaucoma with pressures in this range have been noted to suffer progressive visual field loss within those 5 years. In contrast, in the few studies in which mean pressures of 13 mm Hg or lower were achieved, the risk of progressive visual field loss is reported to be only 6% to 18%. Previous reports of the use of low-dose 5-fluorouracil and of mitomycin in primary filtering surgery have shown that they yield lower mean pressures. For instance, in a prospective, randomized multicenter study, eyes treated with postoperative 5-fluorouracil achieved significantly lower pressures and required fewer postoperative antiglaucoma medications than control eyes.

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PATIENTS AND METHODS

Approval for the study was obtained from the Medical Sciences’ Subcommittee for the Protection of Human Subjects at the University of Miami School of Medicine, Miami, Fla. A standardized surgical technique was used in all consecutive patients who underwent primary filtering surgery, performed by one of us (P.F.P.), at the Bascom Palmer Eye Institute, Miami, between April 1, 1991, and December 31, 1994. Guarded filtration procedures were performed following the administration of regional anesthesia and preparation with povidone-iodine. Incisions of the conjunctiva and Tenon capsule were made in the superior quadrant, 10 mm posterior to the surgical limbus, to create a limbus-based flap. Meticulous hemostasis was achieved with bipolar cautery. A half-thickness, rectangular, 2.5 × 1.0-mm scleral miniflap was outlined at the surgical limbus. In all cases, mitomycin, 0.5 mg/mL, was applied for 5 minutes with a saturated surgical spear (Weck Cel, Weck Ophthalmics, Jacksonville, Fla) that was placed on the sclera while the conjunctiva and Tenon flap were pulled firmly over the sponge with nontoothed forceps. Copious irrigation was then performed with saline solution. A clear corneal paracentesis was placed temporally. A corneal safety valve incision was created as prophylaxis against postoperative hypotony by making a 1.0-mm clear corneal tunnel anterior to the base of the scleral flap.27,28 A 0.75-mm Kelly-Desmarct punch (Storz Ophthalmics, St Louis, Mo) was used to remove an internal block of clear corneal tissue from the posterior lip of the anterior chamber entry site. Wound resistance was adjusted by taking additional partial bites with the punch until an estimated IOP of 4 to 6 mm Hg was achieved. The scleral flap was then reapposed with 2 to 3 interrupted 10-0 monofilament nylon sutures, and the scleral flap resistance was adjusted to achieve an estimated IOP at equilibrium flow of 8 to 12 mm Hg. The limbus-based conjunctival incision was closed with a running 10-0 nylon suture on a needle (CU-5, Alcon, Ft Worth, Tex). Additional balanced salt solution was placed into the anterior chamber to re-form the filtering bleb and to monitor for leaks. No subconjunctival injections were administered, and the eye was patched after the administration of topical neomycin sulfate, polymyxin B sulfate, and 0.1% dexamethasone ointment. Postoperatively, 1% prednisolone acetate was prescribed every 2 hours for the first week, with gradual tapering over several months, and 1% atropine sulfate was prescribed twice daily for 1 to 2 weeks. Ointment (0.1% dexamethasone) was administered nightly for 2 weeks.

Demographic and clinical data were abstracted from the medical records of those patients who underwent primary trabeculectomy. Excluded from the overall study analysis were 15 eyes deemed to be at high risk for trabeculectomy failure (eyes with glaucoma associated with anterior segment neovascularization, uveitis, and the iridocorneal endothelial syndrome, as well as eyes with juvenile glaucoma).

For those patients who underwent a trabeculectomy in both eyes during the study period, data relating to only the first eye were included in this study. Clinic visits from 9 through 18 months postoperatively were analyzed as 1-year postoperative visits, and clinic visits from 18 through 30 months postoperatively were analyzed as 2-year postoperative visits.

The best-corrected visual acuity status was summarized in logMAR units, which equals −log(MAR), where MAR indicates the numerator of visual acuity divided by the denominator of visual acuity. Visual acuities classified as counting fingers, hand motions, light perception, and no light perception were assigned values of 1.000/200, 0.500/200, 0.250/200, and 0.125/200, respectively.29

In this study, a “successful” trabeculectomy was defined as a trabeculectomy that resulted in an IOP of 21 mm Hg or lower and a 30% or greater reduction in IOP at 1 or 2 years of follow-up, with or without medications, and without a reoperation for an elevated IOP. Trabeculectomy survival rates between patient subgroups were compared using Kaplan-Meier survival analysis (log-rank test).30

The few published studies that report the efficacy of mitomycin when used during a primary trabeculectomy are limited by a small sample size, a short length of follow-up, or both.17-19,21-26 Our study investigates the efficacy and safety of intraoperative mitomycin when used during a primary trabeculectomy within a larger series of consecutive patients at 1 and 2 years postoperatively.

RESULTS

Data concerning 89 patients were included in this study. One-year follow-up data were available for 68 patients, and 2-year follow-up data were available for 56 patients. The characteristics of the study patients are shown in Table 1.

To seek evidence of bias in our study due to the lack of follow-up for all patients, the 68 patients with at least 1 year of follow-up were compared with the 21 patients with less than 1 year of follow-up; no statistically significant differences in age, sex, race, preoperative IOP, number of preoperative glaucoma medications, or number of previous laser treatments for glaucoma were found between the 2 groups. However, the median preoperative visual acuity was somewhat worse among patients with less than 1 year of follow-up than among patients with at least 1 year of follow-up (20/80 vs 20/30, P < .001, Mann-Whitney U test).

The types of glaucoma treated were as follows: primary open-angle glaucoma, 69 (77.5%) of the patients; secondary open-angle glaucoma, 1 (1.1%) of the patients; chronic angle-closure glaucoma, 7 (7.9%) of the patients; mixed-mechanism glaucoma, 2 (2.2%) of the patients; angle-recession glaucoma, 3 (3.4%) of the patients; pseudoexfoliation, 5 (5.6%) of the patients; and pigmentary glaucoma, 2 (2.2%) of the patients. Table 2 shows the IOP results at 1 and 2 years postoperatively after primary trabeculectomy with the use of adjunctive intraoperative mitomycin. At 1 and 2 years postoperatively, the proportion of patients with an IOP of 15 mm Hg or lower was 62 (91.2%) of 68 patients and 47 (83.9%) of 56 patients, respectively.

Visual acuity changes among the patients during the study period are displayed in Table 3. The number of patients with a visual acuity on a standard Snellen visual acu-
ity chart within 0.3 logMAR units (less than a doubling of the visual angle) of their preoperative visual acuity at 1 and 2 years postoperatively was 61 (89.7%) of 68 patients and 46 (83.6%) of 55 patients, respectively.

Table 4 demonstrates the results of a Kaplan-Meier survival analysis, which adjusts for different lengths of follow-up. Success rates using various definitions of success are demonstrated in Table 4.

Trabeculectomy failed in 14 of the 89 patients during the study period. Seven trabeculectomies were considered failures because the postoperative IOP reduction was less than 30%; in 3 patients, the postoperative IOP was higher than 21 mm Hg; and 4 failures were due to reoperations for inadequate IOP control. Reoperations were performed between 3 and 17 months after the first trabeculectomies.

Nine patients underwent needle elevation of the scleral flap between 2 days and 6 months after filtration surgery for pressures between 20 and 54 mm Hg, using a technique previously described.31 In 2 patients, a further glaucoma procedure was performed. As in the Fluorouracil Filtering Surgery Study,11 scleral flap needling was not considered a reoperation, as this is an office procedure that does not require the patient to return to the operating room.

The results of univariate survival analyses investigating the associations between trabeculectomy failure and age, race, type of glaucoma, preoperative IOP, preoperative visual acuity, number of preoperative glaucoma medications, and previous laser treatments are shown in Table 5. The only baseline variable examined that was statistically significant was race (P=.03, log-rank test). No statistically significant differences were found between younger (<50 years) and older (≥50 years) patients, between patients with high (≥25 mm Hg) and low (<25 mm Hg) preoperative pressures, between those with a poor (<20/40) and a good (≥20/40) visual acuity, between those with and without prior laser treatment, or between those using more (>2) and those using fewer (≤2) glaucoma medications.

The complications of primary trabeculectomy with the use of adjunctive intraoperative mitomycin were as follows: endophthalmitis, 2 (2.2%) of the patients; hy-
Although intraoperative mitomycin has been shown to improve the success of trabeculectomy in eyes with a high risk of surgical failure, the few published studies that report the efficacy of mitomycin when used during a primary trabeculectomy are limited by a small sample size, a short length of follow-up, or both. In this study of consecutive primary trabeculectomies performed by one of us (P.F.P.), intraoperative mitomycin was associated with a 78% (at 2 years) to 86% (at 1 year) success rate, even with a rather stringent definition of success. In addition to reducing the mean IOP 13 mm Hg or more at 1 and 2 years postoperatively, primary trabeculectomy with the use of adjunctive intraoperative mitomy-
cin greatly reduced the need for glaucoma medication. Although quality of life was not assessed in this study, decreasing the need for glaucoma medication may be associated with improved quality of life by decreasing toxic and unpleasant side effects of such medication. Further, a decreased need for medication has cost implications and is particularly important for patients with poor compliance with medical therapy.

The goal of glaucoma filtration surgery is to slow or eliminate pressure-dependent retinal ganglion cell loss during the lifetime of the patient. Unfortunately, the usual trabeculectomy without an antifibrotic agent yields pressure control in the upper normal pressure range, at which one third to one half of patients will suffer additional visual field loss within 5 years. Furthermore, in half of the cases, filtration must be supplemented by the reinstitution of medical therapy to achieve even that level of control, meaning that patients unable or unwilling to use medical therapy have an even worse prognosis.

Evidence has been accumulating that a dose-response relationship exists between the mean IOP obtained after filtration surgery and the risk of further visual field loss (Table 6). Similar dose-response relationships between IOP and progressive visual field loss have been reported for mixed medical-surgical therapy in patients with advanced glaucoma by Odberg and in patients with early glaucoma by Mao et al.

In an effort to achieve low to normal pressures, we employed antifibrotic agents in primary filtering surgery. Between 1984 and 1991, we performed primary filtering surgery with 5 injections of 5-fluorouracil in numerous eyes and observed a significantly lower mean IOP than in comparable or lower-risk eyes operated on without 5-fluorouracil. The mean IOP at 1 year was 10.9 mm Hg with 5-fluorouracil and 15.0 mm Hg without it. In addition, at 18 months, the rate of failure by the usual criteria (IOP > 20 mm Hg and taking medication) was 17% without 5-fluorouracil vs 5% with it, the percentage of patients requiring medical therapy was 33% vs 11%, and the percentage of patients reaching our goal of an IOP lower than 16 mm Hg without medication was 33% vs 81%. These results are consistent with those found through a prospective, randomized, multicenter study of 5-fluorouracil in patients undergoing primary trabeculectomy.

### Table 4. Success Rates of Primary Trabeculectomy With the Use of Adjunctive Intraoperative Mitomycin, Using Survival Analysis (N=89)*

<table>
<thead>
<tr>
<th>Postoperative Year</th>
<th>Success Rate (SE)†</th>
<th>Success Rate (SE)‡</th>
<th>Success Rate (SE)§</th>
<th>Success Rate (SE)¶</th>
<th>Success Rate (SE)‖</th>
<th>Success Rate (SE)¶¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>85.4 (0.04)</td>
<td>95.7 (0.02)</td>
<td>92.7 (0.03)</td>
<td>83.9 (0.04)</td>
<td>89.8 (0.04)</td>
<td>82.4 (0.05)</td>
</tr>
<tr>
<td>2</td>
<td>77.9 (0.05)</td>
<td>93.9 (0.03)</td>
<td>89.1 (0.04)</td>
<td>74.6 (0.06)</td>
<td>80.6 (0.05)</td>
<td>69.3 (0.06)</td>
</tr>
</tbody>
</table>

*All success rates are given as the percentages.†Success was defined as patients without a reoperation and with an intraocular pressure of 21 mm Hg or lower and a 30% or more reduction in intraocular pressure, with or without medications.‡Success was defined as patients without a reoperation.§Success was defined as patients without a reoperation and with an intraocular pressure of 21 mm Hg or lower, with or without medications.¶Success was defined as patients without a reoperation and with an intraocular pressure of 21 mm Hg or lower, without medications.‖Success was defined as patients without a reoperation and with an intraocular pressure of 15 mm Hg or lower, with or without medications.¶¶Success was defined as patients without a reoperation or scleral flap needling, with an intraocular pressure of 15 mm Hg or lower, and without medications.
comes in eyes following initial trabeculectomy supplemented intraoperatively with 5-fluorouracil or mitomycin. In 1 study of high-risk filtering procedures, the pressure-lowering effect was more persistent with mitomycin than with 5-fluorouracil, with a mean follow-up of 32 months. Further follow-up is needed to determine if this is also true in primary filtering surgeries.

The overall benefit to visual function by a greater IOP reduction at 5 years was demonstrated for the use of 5-fluorouracil in complex filtering surgery and may be even more favorable for the use of mitomycin than for 5-fluorouracil in complex filtering surgery and combined procedures. It has yet to be proved that the benefit-risk ratio for the use of antifibrotic agents in primary filtering surgery will also be favorable. While precise estimates of incidence rates are difficult to determine without a larger series, there is increasing concern about a seemingly higher rate of endophthalmitis and hypotony after filtering surgery with the use of adjunctive mitomycin. In our study, endophthalmitis occurred in 2 (2.2%) of the patients. Furthermore, although in this series the final visual outcomes of patients with hypotonia were quite good, it is important to note that 4 (4.5%) of the patients underwent revision for hypotonia.

The success and compiliation rates reported in this study were obtained for the use of adjunctive mitomycin, 0.5 mg/mL, for 5 minutes; inferences about the results using a lower dose of mitomycin cannot be made based on the data provided in this study. Few glaucoma surgeons use 0.3-mg/mL applications of mitomycin for 5 minutes in primary trabeculectomies. In fact, results comparable with those in our study have been reported for the use of adjunctive mitomycin, 0.2 mg/mL, for 3 to 5 minutes. The surgeon (P.F.P.) whose patient series is reported in this study is using mitomycin, 0.4 mg/mL, for 2 minutes in primary trabeculectomies.

In our study, primary trabeculectomy with the use of adjunctive intraoperative mitomycin lowered the IOP by at least 30% in approximately 78% (at 2 years) to 86% (at 1 year) of the cases and was associated with a marked reduction in the percentage of patients who required glaucoma medication. There was a significantly (P<.03) lower success rate in black patients. Because trabeculectomy

### Table 5. Baseline Clinical Variables and Success Rates of Primary Trabeculectomy With the Use of Adjunctive Intraoperative Mitomycin, Using Survival Analysis (Categorical Variables)*

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Success Rate at 1 Year (2 Years), %†</th>
<th>No. of Patients (N=89)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>76.2 (54.4)</td>
<td>20</td>
<td>.03‡</td>
</tr>
<tr>
<td>Hispanic</td>
<td>90.9 (87.1)</td>
<td>41</td>
<td>.08§</td>
</tr>
<tr>
<td>White</td>
<td>82.6 (77.1)</td>
<td>28</td>
<td>...</td>
</tr>
<tr>
<td>Hispanic-white</td>
<td>87.5 (83.0)</td>
<td>69</td>
<td>...</td>
</tr>
<tr>
<td><strong>Type of glaucoma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POAG</td>
<td>84.7 (74.7)</td>
<td>69</td>
<td>.38</td>
</tr>
<tr>
<td>20AG</td>
<td>...</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>CAGC</td>
<td>80.0 (80.0)</td>
<td>7</td>
<td>...</td>
</tr>
<tr>
<td>Mixed mechanism</td>
<td>100.0 (100.0)</td>
<td>2</td>
<td>...</td>
</tr>
<tr>
<td>Angle recession</td>
<td>100.0 (100.0)</td>
<td>3</td>
<td>...</td>
</tr>
<tr>
<td>Pseudoexfoliation</td>
<td>75.0 (75.0)</td>
<td>5</td>
<td>...</td>
</tr>
<tr>
<td>Pigmentary</td>
<td>100.0 (100.0)</td>
<td>2</td>
<td>...</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>83.3 (83.3)</td>
<td>10</td>
<td>.73</td>
</tr>
<tr>
<td>≥50</td>
<td>85.5 (77.2)</td>
<td>79</td>
<td>...</td>
</tr>
<tr>
<td><strong>Preoperative intraocular pressure, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>79.0 (69.5)</td>
<td>49</td>
<td>.07</td>
</tr>
<tr>
<td>≥25</td>
<td>93.6 (89.2)</td>
<td>40</td>
<td>...</td>
</tr>
<tr>
<td><strong>Preoperative visual acuity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20/40</td>
<td>86.5 (77.4)</td>
<td>59</td>
<td>...</td>
</tr>
<tr>
<td>&lt;20/40</td>
<td>81.9 (81.9)</td>
<td>30</td>
<td>...</td>
</tr>
<tr>
<td><strong>No. of prior laser treatments</strong></td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>77.8 (70.0)</td>
<td>25</td>
<td>...</td>
</tr>
<tr>
<td>&gt;0</td>
<td>88.1 (85.7)</td>
<td>64</td>
<td>...</td>
</tr>
<tr>
<td><strong>No. of preoperative glaucoma medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>92.7 (83.5)</td>
<td>33</td>
<td>...</td>
</tr>
<tr>
<td>&gt;2</td>
<td>80.6 (74.4)</td>
<td>56</td>
<td>...</td>
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</table>

*POAG indicates primary open-angle glaucoma; 20AG, secondary open-angle glaucoma; CAGC, chronic angle-closure glaucoma; and ellipses, data not available.
†No reoperation, an intraocular pressure of 21 mm Hg or lower, and a 30% or greater reduction in intraocular pressure, with or without glaucoma medications.
‡Value for black patients compared with all other patients.
§Value for Hispanic patients compared with all other patients.
||Value for patients with POAG compared with all other patients.

In the present study, the mean IOP after 2 years was 11.9 mm Hg (Table 2), the number of patients not taking supplemental medication was 60 (88.2%) of 68 patients at 1 year and 47 (83.9%) of 56 patients at 2 years (Table 2), the rate of failure (an IOP >21 mm Hg, a <30% reduction in IOP, or a reoperation for an elevated IOP) was 14.6% at 1 year and 22.1% at 2 years (Table 4), and the percentage of patients reaching the conservative goal of an IOP of 15 mm Hg or lower without medication or a reoperation was 82.4% at 1 year and 69.3% at 2 years (Table 4).

Thus, it seems that the improvement in success rates by various criteria (mean IOP and percentage of patients with an IOP of 15 mm Hg or lower without medication) in our patient population was comparably improved at 18 to 24 months of follow-up by the use of either 5 injections of 5-fluorouracil or intraoperative mitomycin. Similarly, Smith et al reported comparable out-
may fail at any time postoperatively, continued careful follow-up is necessary. Successful lowering of the IOP with the use of adjunctive intraoperative mitomycin must be considered in light of such risks as endophthalmitis and hypotony.

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