Incidence of Late-Onset Bleb-Related Complications Following Trabeculectomy With Mitomycin

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**Objectives:** To determine the incidence of late-onset bleb-related complications following trabeculectomy with mitomycin and to report the management and outcome of bleb leaks following trabeculectomy with mitomycin.

**Methods:** A retrospective medical record review of all patients who underwent trabeculectomy with mitomycin from June 1, 1991, through April 30, 1998, at our institution was performed. The Kaplan-Meier survival method was used to estimate the probability of (1) endophthalmitis, (2) blebitis, (3) a bleb leak, and (4) the combined outcome (the first occurrence of a bleb leak, blebitis, or endophthalmitis). This survival analysis included only the first trabeculectomy in an eye, with at least 3 months of follow-up during the study period. A separate description of bleb leak management and outcome was performed.

**Results:** Two hundred thirty-nine eyes of 198 patients were included in the survival analysis. The average follow-up was 2.7 (range, 0.3-7.3) years. Twenty eyes (8%) from 19 patients experienced a bleb leak; the adjusted incidence was 3.2% per patient-year. Five eyes (2%) had an episode of blebitis. Eight eyes (3%) experienced an episode of endophthalmitis; the follow-up adjusted incidence (number of events per patient-year) was 1.3%. Twenty-seven eyes (11%) from 26 patients had at least 1 of the complications of a bleb leak, blebitis, or endophthalmitis; the adjusted incidence was 4.4% per patient-year. A Kaplan-Meier analysis estimated the 5-year probability of developing a bleb leak, blebitis, or endophthalmitis to be 17.9%, 6.3%, and 7.5%, respectively. Two hundred fifty-eight trabeculectomies in 242 eyes of 198 patients were included in the description of bleb leak management and outcome. Bleb leaks occurred in 22 eyes (9% of the 258 trabeculectomies). Seventeen eyes were successfully treated with office-based measures, and 4 ultimately underwent surgical bleb revision. One eye without infection continued to leak after 11 months of office-based therapy.

**Conclusions:** There is significant morbidity associated with a trabeculectomy with mitomycin. The incidence of a bleb leak or an infection continues at a fairly constant rate over time, such that at 5 years, up to 23% of all patients might develop one of these complications. An isolated bleb leak seems to be a relatively benign condition, as three quarters resolve with office-based methods.

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**TRABECULECTOMY remains the standard of care for patients who have failed maximal tolerated medical therapy. Risk factors, such as previous surgery, age, and race, may predispose patients to bleb failure if an antifibrotic agent is not used with trabeculectomy. The use of intraoperative mitomycin as an adjunct to standard trabeculectomy has increased the likelihood that this procedure will maintain low intraocular pressures.**

**Mitomycin inhibits the postoperative scarring response by cross-linking the DNA in the conjunctival and episcleral fibroblasts to which it is exposed, decreasing their ability to proliferate. While this technique produces thinner blebs that provide enhanced filtration, it also leads to an increased incidence of postoperative hypotony, bleb leak, and endophthalmitis.**

Bleb leaks place patients at risk of developing endophthalmitis and are, therefore, considered a significant late postoperative complication. We are not aware of a study that has described the incidence and outcome of late-onset bleb leaks. We undertook a retrospective review of patients undergoing trabeculectomy with mitomycin to determine the incidence of late-onset endophthalmitis and the incidence and outcome of late postoperative bleb leaks.

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PATIENTS AND METHODS

Medical records were reviewed for all patients who underwent trabeculectomy with mitomycin from June 1, 1991, through April 30, 1998, at our institution. A standard surgical technique using a superior limbal-based incision encompassed most procedures. Mitomycin, most commonly 0.5 mg/mL, was applied for periods ranging from 30 seconds to 5 minutes based on the patient’s age, race, and number of prior operations. Data from 285 trabeculectomies performed in 266 eyes of 219 patients were examined. Attempts were made to collect as much follow-up information as possible from referring physicians who resumed postoperative care. Minimal acceptable information for each patient included any surgical interventions during the study period, demographics, visit date, and slitlamp examination findings indicating the presence of endophthalmitis, blebitis, or a late bleb leak. Blebitis was defined as localized anterior segment inflammation with mucopurulent material in or around the bleb, usually with anterior chamber cells but without a hypopyon. An infection was considered endophthalmitis when a hypopyon or vitreous inflammation was present. A late bleb leak was defined as a positive leak by Seidel test result that occurred at least 3 months after the initial surgery. This interval was chosen to avoid inclusion of bleb leaks that were related to the initial surgery.

RESULTS

Data from 285 trabeculectomies performed by 1 of 3 different surgeons (T.W.P., G.H. or P.K.) in 266 eyes of 219 patients were examined. Twenty-seven operations in 27 eyes of 25 patients were excluded from the study because either no follow-up information from the referring physicians (8 operations in 8 eyes of 7 patients) or less than 3 months of postoperative follow-up information (19 operations in 19 eyes of 18 patients) was available. Nineteen operations in 18 eyes of 17 patients represented a second or later operation on a particular eye during the study period. These 19 subsequent operations were excluded from the survival analysis but were included in the description of bleb leak management and outcome.

SURVIVAL ANALYSIS

A total of 239 eyes from 198 patients were included in the survival analysis. Demographics are shown in the Table. The failure estimates (1−survival) are shown in the Figure. The mean postoperative follow-up was 2.7 years (range, 0.3–7.3 years). Twenty eyes (8%) developed a bleb leak. The follow-up-adjusted incidence was 3.2% per patient-year. The Kaplan-Meier estimates of developing a bleb leak at 1 and 5 years were 1.3% (95% CI, 0.4–11.8) at 5 years. Eight eyes (3%) had an episode of endophthalmitis at 1 and 5 years, respectively (Figure). Plots of the cumulative hazards (cumulative hazard = −log [survival]) vs time appear linear and, thus, suggest that the hazard (or probability of failure in the next instant) was relatively constant during follow-up.

MANAGEMENT AND OUTCOME

A total of 258 trabeculectomies in 242 eyes of 198 patients were considered in the description of bleb leak management and outcome. Twenty-two trabeculectomies (9%) from 21 patients experienced bleb leaks. Two of these trabeculectomies were excluded from the survival analysis because they occurred in eyes after a second operation. Seventeen eyes were successfully treated with conservative measures, and 4 ultimately underwent surgical bleb revision. One eye without signs of blebitis or endophthalmitis continued to leak after 11 months of conservative therapy. Thirteen (59%) of the 22 bleb leaks resolved with antibiotic prophylaxis alone, with an average leak duration of 55 days (range, 3–230 days). Other therapies included mircrylate tissue adhesive (n = 3), trichloroacetic acid topical

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application (n=4), cryotherapy (n=1), bandage contact lens (n=3), and autologous blood patch (n=1). In some cases, it was difficult to determine which therapy contributed to the final resolution of the leak because a series of treatments was undertaken before the leak resolved. Of the 22 eyes that experienced a leak, 8 (36%) had 1 or more bleb leak recurrences, with an average of 0.6 recurrences per eye (range, 0-3 recurrences per eye). Most bleb leaks were in asymptomatic patients. However, bleb leaks were diagnosed in 5 patients who were seen with a clinical picture consistent with blebitis, and 1 had a concurrent leak and endophthalmitis. One patient with a bleb leak treated with antibiotic prophylaxis for 1 month developed an infection (blebitis vs early endophthalmitis). Blebitis did not progress to endophthalmitis in any of the patients treated with topical antibiotics.

Our study demonstrates that there is significant morbidity associated with a trabeculectomy with mitomycin. Based on the follow-up adjusted incidence, 1 of every 100 patients developed endophthalmitis each year, and 4% of patients each year developed a bleb-related complication consisting of a bleb leak, blebitis, or endophthalmitis. This incidence continued at a fairly constant rate over time, such that at 5 years, 23% of all patients would be predicted to develop one of these bleb-related complications.

An isolated bleb leak seems to be a relatively benign condition. Early in the study, bleb leaks were treated more aggressively with measures such as mercrulate glue, cryotherapy, and contact lenses. Because of the small sample size, it is difficult to determine whether any of these conservative measures were superior to the others. However, as it became apparent that leaks often resolved without these interventions, a less aggressive approach was adopted and leaks underwent only antibiotic

### Demographic Characteristics

<table>
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<tr>
<th>Characteristic</th>
<th>Bleb Leak (20 Eyes of 19 Patients)</th>
<th>Blebitis (5 Eyes of 5 Patients)</th>
<th>Endophthalmitis (8 Eyes of 7 Patients)</th>
<th>Bleb Leak, Blebitis, or Endophthalmitis (27 Eyes of 26 Patients)</th>
<th>All Cases (239 Eyes of 198 Patients)</th>
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<tr>
<td>Age, y</td>
<td>Mean ± SD 54.9 ± 17.3</td>
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<td>Follow-up, y</td>
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*Data are given as number of eyes unless otherwise indicated.

Kaplan-Meier estimates of the probability of failure by bleb leak, blebitis, or endophthalmitis alone or in combination. CI indicates confidence interval; ellipses, data not applicable.
treatment for months. Further management was only undertaken if there was hypotony with a shallow anterior chamber, hypotony maculopathy, or other factors that might increase the risk of infection, such as recurrent bacterial conjunctivitis, severe blepharitis, or dry eye. Only 1 patient developed endophthalmitis while being followed up regarding a leaking bleb. Our patients were routinely treated with prophylactic antibiotics while experiencing a leak, typically with gentamicin sulfate; it was thought that the conjunctival irritation produced might encourage a healing response. There is no direct evidence that antibiotics decrease the risk of infection or speed wound healing, and not all clinicians use them.

Endophthalmitis is typically manifest with significant symptoms that bring cases to the attention of a physician. Bleb leaks, on the other hand, are often asymptomatic and, therefore, the true incidence is somewhat difficult to determine. These data likely underreport the actual incidence of bleb leaks in functioning filters for 2 reasons. First, we included all eyes that underwent trabeculectomy with mitomycin, even those that ultimately developed scarred nonfunctioning blebs with no significant risk of leaking. If only functioning blebs were considered, the denominator would be smaller and the incidence of endophthalmitis and bleb leaks would be larger. Second, some bleb leaks may not have been observed because leaks are frequently asymptomatic and Seidel testing was not routinely performed on all patients. The clinical indication for Seidel testing was an ischemic thin bleb with a suspicious appearance or low pressure. Because some asymptomatic leaks were likely to be missed, our numerator is expected to be smaller than the number of actual leaks, which would also lead to an underestimation of the overall incidence.

Several similar studies have reported information on endophthalmitis and bleb leaks. Greenfield et al reported the incidence of endophthalmitis after superior trabeculectomy with mitomycin (in 251 eyes) to be 1.6% (4 episodes), with a mean follow-up of approximately 16 months. The adjusted incidence (events per patient-year) was 1.3% after superior trabeculectomy. We also estimate an adjusted incidence of 1.3% per patient-year.

Higginbotham et al reported on bleb-related endophthalmitis after mitomycin administration in 229 eyes of 192 patients, with a mean of 18½ months of follow-up. Of 179 eyes that underwent superior trabeculectomy with mitomycin, 2 developed endophthalmitis, for an overall rate of 1.1%. Survival curve analysis of the whole patient group, including the inferior filtering sites (4 of 6 cases of endophthalmitis), at 2½ years after surgery estimated the probability of developing endophthalmitis to be 4.8%. Our estimate at 2½ years was lower, 2.4% (95% CI, 0.4-4.8), but included mainly superior filters.

There is less comparable information regarding bleb leaks. A large study of bleb leak prevalence by Greenfield et al found 10 (3.7%) of 273 trabeculectomies with mitomycin to have a leak during 2½ months of examinations. A smaller study on a slightly different category—sequential multifocal bleb leaks—by Belyea et al showed sequential multifocal leaks in 2 (1%) of 192 eyes after trabeculectomy with mitomycin, with 20.4 months of follow-up. This study supports our finding that bleb leaks often recur following resolution of the initial leak. We observed 22 bleb leaks (9%) of 258 trabeculectomies, including bleb leaks that occurred after a second operation during the study period. At 5 years, there is almost a 20% risk of developing a bleb leak. This information is disturbing, particularly in young patients who may have 40 or 50 years of life remaining after their filtering procedure.

Only 1 patient in our study developed an infection while being followed up regarding a leaking bleb. A recent article by Soltau et al confirmed the clinical impression that a bleb leak is a risk factor for infection. In a case-control study, a multivariate analysis found the odds of a leak in a patient in the bleb-related infection group to be 25.8 times the odds of a leak in a patient in the control group. Variables other than bleb leak found to be risk factors for infection were younger age, black race, and inferior bleb location.

The limitations of this study include its retrospective nature and the lack of complete follow-up on all patients. In addition, all patients did not undergo Seidel testing of the blebs at each follow-up visit unless clinically indicated.

Within the limits of this study, it may be concluded that the incidence of endophthalmitis associated with filtering blebs after mitomycin administration is approximately 1.3% per year. The risk of developing at least 1 complication (a bleb leak, blebitis, or endophthalmitis) remains relatively stable during the first 5 years after surgery, with an annual incidence of approximately 4.4%. There seems to be no period when filtered eyes are more or less vulnerable to these complications. Bleb leaks seem to be safely managed with conservative interventions over long periods. In some cases, surgical intervention is necessary.

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