Late-Onset Bleb Leaks After Glaucoma Filtering Surgery

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**Objective:** To determine the incidence of focal, late-onset, conjunctival bleb leaks after glaucoma filtering surgery.

**Design:** Prospective, cross-sectional analysis.

**Setting:** Tertiary care outpatient referral center.

**Patients:** Consecutive patients who underwent glaucoma filtering surgery prior to June 1996 presenting for evaluation from September 2, 1996, through November 15, 1996. Five hundred twenty-five eyes of 525 consecutive patients were enrolled in the study.

**Intervention:** Bleb height (elevated or flat), area (diffuse or localized), and wall thickness (thin, thick, or encapsulated) were classified. Each bleb was tested for focal leakage using a moistened fluorescein strip, cobalt blue illumination, and slit-lamp biomicroscopy. Diffuse transconjunctival aqueous flow did not qualify as a focal leak.

**Main Outcome Measures:** Seidel-positive aqueous leakage.

**Results:** Bleb leakage occurred in 14 eyes following trabeculectomy (mitomycin C treatment, 10 eyes; 5-fluorouracil treatment, 3 eyes; no antifibrosis agent, 1 eye) and in 1 eye following combined cataract and glaucoma surgery with adjunctive mitomycin C therapy. Bleb leakage occurred more frequently in eyes that received mitomycin C (10 [3.7%] of 273 eyes) than 5-fluorouracil (3 [1.4%] of 213 eyes) or no antifibrosis agent (1 [2.6%] of 39 eyes), using Kaplan-Meier estimates (*P* = .008, log-rank test). Conjunctival blebs were significantly thinner after trabeculectomy with mitomycin C than with 5-fluorouracil (*P* = .001). Bleb wall thickness was greater following combined cataract and glaucoma surgery than following trabeculectomy alone (*P* = .008). Age (*P* = .84), sex (*P* = .68), race (*P* = .77), duration of mitomycin C exposure (*P* = .62), number of antiglaucoma medications (*P* = .16), and total 5-fluorouracil dose (*P* = .85) were not associated with late-onset leaks.

**Conclusions:** The risk of late-onset focal bleb leakage increases following trabeculectomy with mitomycin C therapy. Late leakage after combined cataract and glaucoma surgery is infrequent.


**Aqueous leakage from a conjunctival filtering bleb may occur as an early or late complication of glaucoma filtration surgery.** If the leakage is left untreated, vision-threatening complications may result, including ocular hypotony and maculopathy, shallowing of the anterior chamber, peripheral anterior synechiae, cataract formation, corneal decompensation, choroidal effusion, suprachoroidal hemorrhage, and endophthalmitis. Although many treatment options have been proposed, successful closure of late bleb leaks following glaucoma filtering surgery remains a controversial and challenging management problem.

The reported rate of bleb leakage after filtration surgery varies widely and is affected by study sample size, surgical technique, duration of follow-up, and definition of aqueous leakage. Many reports do not distinguish the incidence of early perioperative wound leaks from late-onset leakage, which is associated with a thin, avascular conjunctiva. In addition, Susanna et al reported markedly different rates of aqueous leakage in a study comparing spontaneous bleb leakage with leakage after provocation using ocular digital massage (0% and 31%, respectively).

Although the conjecture is unproven, bleb leakage is thought to be more frequent in eyes that have received perioperative antifibrosis agents. Bleb leaks in eyes treated with 5-fluorouracil or mitomycin C may occur in 5% to 30% of patients. Leaks in these eyes may take longer to heal because of the thin, avascular tissue and associated abnormal fibrovascular response. Histopathological examination of blebs after trabeculectomy with mitomycin C treatment reveals irregularities in the

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PATIENTS AND METHODS

All patients filtered prior to June 1996 and seen in the private practices of D.S.G., J.M.L., and R.R. at The New York Eye and Ear Infirmary, New York, from September 2, 1996, to November 13, 1996, were enrolled in the study. Each patient had undergone previous trabeculectomy (with or without antifibrosis agents) or combined trabeculectomy (with or without antifibrosis agents), cataract extraction, and intracocular lens implantation by 1 of the aforementioned surgeons. If both eyes had undergone filtering surgery, the right eye was enrolled.

Trabeculectomy was performed at the superior limbus using either a limbus-based or fornix-based approach following regional anesthesia and povidone-iodine preparation. Miticulous hemostasis was achieved with light bipolar cautery. A half-thickness scleral flap was outlined at the surgical limbus. Intraoperative mitomycin C (0.5 mg/mL) or 5-fluorouracil (50 mg/mL) was applied to eyes at risk for trabeculectomy failure for variable intervals using a saturated surgical spear (Weck-Cel, Weck Ophthalmics, Jacksonville, Fla) placed between the scleral flap and Tenon fascia, after which conjunctival irrigation with balanced salt solution was performed. A clear corneal param centesis track was made at 90° from the filtration site. Using a 0.75-mm Kelly Descemet punch (Storz Ophthalmics, St Louis, Mo), an internal block of clear corneal and trabecular meshwork tissue was removed. A peripheral iridectomy was performed and the scleral flap was sutured with 2 to 4 interrupted 10-0 monofilament nylon sutures. Limbus-based conjunctival incisions were closed with either a running 10-0 nylon suture or a 9-0 polyglactin suture on a vascular needle. Fornix-based conjunctival incisions were closed with 2 to 3 10-0 nylon sutures. Additional balanced salt solution was injected into the anterior chamber to re-form the filtering bleb and to verify that the wound was watertight. Subconjunctival injections of gentamicin sulfate (20 mg) and methylprednisolone sodium succinate (20 mg) were administered and the eyes were patched following topical application of a combined steroid and antiinflammatory neomycin sulfate, polymyxin B sulfate, and 0.1% dexamethasone. When 5-fluorouracil was used, variable numbers of subconjunctival injections (5 mg per injection) were administered (a 30-gauge needle attached to a 1-mL tuberculin syringe) 180° away from the filtering site during the first 2 postoperative weeks.

Combined cataract and glaucoma surgery was performed using a fornix-based conjunctival incision. In eyes undergoing phacoemulsification, a 3.5-mm wide, half-thickness scleral groove was made approximately 1 mm posterior to the limbus and a scleral tunnel was dissected. In eyes undergoing extracapsular cataract extraction, a half-thickness scleral flap was outlined at the surgical limbus and a 180° superior limbal incision was created. In most eyes, mitomycin C (0.5 mg/mL) or 5-fluorouracil (50 mg/mL) was applied to the surface of the scleral bed for variable intervals. Postoperative subconjunctival infections were administered as previously described.

The clinical examination procedure included characterization of bleb appearance and assessment for bleb leakage, as follows. Under cobalt blue slitlamp illumination, a moistened sterile fluorescein strip was applied to the bleb surface. A leak was defined as a spontaneous focal-point source of aqueous leakage from an area of interrupted conjunctival tissue occurring at least 3 months postoperatively. Diffuse transconjunctival aqueous flow, or “bleb sweat,” did not qualify as a leak. No eyes in this investigation underwent digital massage to enhance visualization of conjunctival leakage.

Blebs were classified by height (elevated or flat), area (diffuse or localized), and wall thickness by 1 of 3 investigators (D.S.G., J.M.L., and R.R.) who were masked to the patients’ surgical histories. Thin-walled blebs were defined as blebs with a transparent conjunctiva where it was possible to visualize the scleral flap or nylon suture. Thick-walled blebs were defined as blebs with a nontransparent conjunctiva. Tenon capsule cysts were classified as encapsulated blebs.

Data abstracted from the patients’ medical records included demographics, glaucoma diagnosis, date and type of glaucoma filtration surgery, previous ocular surgery, type and dose of antifibrosis agent (if applicable), concurrent antiglaucoma medication, and intraocular pressure (IOP). Evaluation of continuous variables was achieved using a Student t test. Categorical variables were evaluated with χ², Fisher exact test, or Spearman rank correlation when appropriate. Statistical significance was determined at P=.05. Each potential confounding variable was screened for association with the outcome. Only those confounding variables that were statistically associated were eligible for the potential final multivariate model.

RESULTS

Five hundred twenty-five eyes of 525 patients were enrolled. Patient demographic data is summarized in Table 1. Bleb leaks were detected in 15 eyes (2.9%). There were no differences in age (P=.84), sex (P=.67), ethnicity (P=.46), glaucoma diagnosis (P=.56), length of postoperative follow-up (P=.27), number of previous conjunctival incisions (P=.25), number of concurrent antiglaucoma medications (P=.13), duration of mitomycin C exposure (P=.79), and total 5-fluorouracil dose (P=.85) in the leaking and nonleaking blebs (Table 2 and Table 3).

Bleb leakage occurred in 14 eyes following trabeculectomy (mitomycin C treatment, 10 eyes; 5-fluorouracil treatment, 3 eyes; no antifibrosis agent, 1 eye) and in 1 eye following combined trabeculectomy with mitomycin C, cataract extraction, and intraocular lens implantation. Bleb leakage occurred more frequently in eyes that received mitomycin C (10 [3.7%] of 273 eyes) than those that received 5-fluorouracil (3 [1.4%] of 213 eyes) or no antifibrosis agent (1 [2.6%] of 39 eyes), using Kaplan-Meier estimates (P=.008, log-rank test) (Figure). The clinical characteristics and bleb appearance in eyes with and without aqueous leakage are described in Table 3. Mean±SD IOP was significantly lower in eyes with bleb leaks (9.5±4.5 vs...
15.4±6.9 mm Hg, P=.001, Student t test). Five (33.3%) of 15 eyes with leaks had an IOP of 14 mm Hg or more.

Compared with nonleaking blebs, leaking blebs were more likely to be characterized as localized and thin-walled (P=.007 [Fisher exact test] and .02 [χ² test], respectively). Leaks occurred in 12 (5.2%) of 231 blebs classified as thin, in 3 (1.1%) of 278 blebs classified as thick, and in 0 of 16 blebs classified as encapsulated. Bleb wall thickness was greater following combined surgery than following trabeculectomy (P=.008).

One hundred eighty-one eyes underwent trabeculectomy with 5-fluorouracil treatment and 170 eyes underwent trabeculectomy with mitomycin C treatment (Table 4). Conjunctival blebs were significantly thinner after trabeculectomy with mitomycin C than with 5-fluorouracil (P=.001, χ² test). The incidence of bleb leakage was significantly greater in eyes after trabeculectomy with mitomycin C than with 5-fluorouracil (3.9% vs 1.7%, P=.05), despite the fact that follow-up was significantly longer in eyes after trabeculectomy with 5-fluorouracil (P<.001). Age, sex, ethnicity, IOP, number of antiglaucoma medications, bleb height, and bleb area were similar both in the eyes that had undergone 5-fluorouracil trabeculectomy and in those that had undergone mitomycin C trabeculectomy.
Bleb leak management included observation (5 eyes); placement of a large-diameter bandage contact lens (4 eyes); combined bandage contact lens placement, autologous blood injection, and compression suture repair (3 eyes); bleb excision and conjunctival advancement (2 eyes); and argon laser treatment following application of methylene blue dye (1 eye).

Aquous leakage from a conjunctival filtering bleb may be classified as early or late. Early-onset bleb leaks, largely dependent on technical aspects of wound closure, generally occur within the first 3 postoperative months. Late-onset leaks are typically associated with thin, cystic, avascular blebs and occur months to years after surgery. In our study, we defined late-onset bleb leaks as those that develop at least 3 months after filtering surgery.

Leaks occur infrequently after trabeculectomy without antifibrosis agents but have been reported in 3.3% of eyes after full-thickness procedures. The reported rate of late-onset bleb leakage after glaucoma filtering surgery using mitomycin C and 5-fluorouracil is highly variable and dependent upon individual wound-healing response, surgical procedure (ie, trabeculectomy vs combined cataract extraction and trabeculectomy), and surgical technique. Differences in sample size, length of follow-up, definition of aqueous leakage, spontaneous or provoked leak detection, and filtering bleb location also affect reported leak rates. The Fluorouracil Filtering Surgery Study Group reported a 12.9% rate of late leakage in eyes with filtering blebs after trabeculectomy with 5-fluorouracil at the inferior limbus. In eyes after trabeculectomy with 5-fluorouracil or mitomycin C, Susanna et al reported an increased rate of late-onset leak detection when digital ocular massage was performed. Others have reported an incidence of late leakage ranging between 4.2% and 10% after trabeculectomy with mitomycin C.

Study design (retrospective or prospective) will also affect the detection rate. Leaks are often only sought in eyes with hypotony, anterior chamber shallowing, choroidal detachment, or suspected infection. As such, retrospective reporting will underestimate the true incidence of leakage. Belyea et al retrospectively reviewed 385 consecutive eyes undergoing trabeculectomy with 5-fluorouracil or mitomycin C treatment and reported a 1.8% overall incidence of late-onset sequential multifocal leaks (5 eyes received 5-fluorouracil, 2 eyes received mitomycin C). Histopathological examination of 3 eyes demonstrated epithelial breakdown, hypocellularity, and stromal collagen necrosis in the bleb. To determine more clearly the incidence of late-onset leakage, we performed a prospective cross-sectional analysis of late-onset leakage among a consecutive series of eyes with filtration blebs with a minimum of 3 months postoperative follow-up.

In this cross-sectional series, we found that bleb leaks occurred 3 times more commonly following trabeculectomy with mitomycin C than after 5-fluorouracil treatment, despite the fact that the duration of follow-up was significantly greater in the 5-fluorouracil–treated group than in the mitomycin C–treated group (P < .001). If these blebs become thinner over time, one would expect a greater rate of late leakage in those eyes with longer follow-up. In contrast, others have retrospectively reported a greater incidence of late leakage after trabeculectomy with 5-fluorouracil. Belyea et al reported a slightly greater rate after filtering surgery with 5-fluorouracil treatment (2.6%) compared with surgery with mitomycin C treatment (1.0%). Katz et al reported 2 (11%) of 19 eyes with late-onset bleb leaks after trabeculectomy.

**Table 4. Clinical Characteristics and Bleb Appearance in Eyes With 5-Fluorouracil vs Mitomycin C Trabeculectomy**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>5-Fluorouracil</th>
<th>Mitomycin C</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>181</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD age, y</td>
<td>63.3 ± 15.2</td>
<td>65.2 ± 15.3</td>
<td>.24†</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>98</td>
<td>91</td>
<td>.91‡</td>
</tr>
<tr>
<td>Female</td>
<td>83</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Race</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>119</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>38</td>
<td>50</td>
<td>.11‡</td>
</tr>
<tr>
<td>Hispanic</td>
<td>20</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD follow-up, y</td>
<td>3.6 ± 2.6</td>
<td>1.7 ± 1.3</td>
<td>.0001†</td>
</tr>
<tr>
<td>Leak present (%)</td>
<td>3 (1.7)</td>
<td>10 (5.9)</td>
<td>.05§</td>
</tr>
<tr>
<td>Mean ± SD IOP, mm Hg</td>
<td>15.7 ± 7.0</td>
<td>14.9 ± 7.7</td>
<td>.33†</td>
</tr>
<tr>
<td>Mean ± SD No. of medications</td>
<td>0.77 ± 0.79</td>
<td>0.64 ± 0.77</td>
<td>.11†</td>
</tr>
<tr>
<td>Bleb height</td>
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</tr>
<tr>
<td>Elevated</td>
<td>114</td>
<td>119</td>
<td>.16‡</td>
</tr>
<tr>
<td>Flat</td>
<td>67</td>
<td>51</td>
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<tr>
<td>Bleb area</td>
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</tr>
<tr>
<td>Diffuse</td>
<td>84</td>
<td>85</td>
<td>.50‡</td>
</tr>
<tr>
<td>Localized</td>
<td>97</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Bleb wall thickness</td>
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</tr>
<tr>
<td>Thin</td>
<td>74</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>Thick</td>
<td>97</td>
<td>69</td>
<td>.001†</td>
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<tr>
<td>Encapsulated</td>
<td>10</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*Values are expressed as number of eyes, unless otherwise indicated. IOP indicates intraocular pressure.  †Values are derived from t test.  ‡Values are derived from χ² test.  §Values are derived from Fisher exact test.

**Kaplan-Meier estimation of bleb survival without development of late-onset leakage. Bleb leaks occurred more frequently in eyes that had received mitomycin C (P = .008, log-rank test).**
with 5-fluorouracil treatment compared with 1 (5%) of 20 eyes with mitomycin C treatment. It is unclear whether a greater number of leaks might have been identified if each patient in these series had been sequentially tested at every follow-up visit.

We found that, in contrast with early-onset bleb leakage, many eyes with late-onset leaks had normal IOP and elevated blebs. Five eyes (33%) with leaks had IOP of 14 mm Hg or greater, implying that IOP alone cannot predict which eyes will have leaks or determine which eyes should be tested for leaks. The value of routine Seidel testing, however, remains unclear. Although bleb leaks have been associated with endophthalmitis, a true causative relationship between the two has yet to be proven. In addition, the management of late bleb leakage is both complex and controversial. The risk-benefit ratio of closing conjunctival leaks, with the attendant risks of IOP elevation and visual loss, needs to be validated in a prospective, randomized fashion.

Bleb leakage was uncommon after combined glaucoma and cataract surgery in our study. Others26-39 have reported low rates of leakage after combined procedures. This is consistent with the infrequent development of hypotony and late endophthalmitis following combined cataract and glaucoma surgery, and reflects the thicker bleb walls present in these eyes.40,41 As expected, localized, thin-walled blebs in this series were more prone to leakage than diffuse blebs with thicker walls. Furthermore, bleb leakage in our series was almost 3 times more common in eyes that had undergone primary filtering surgery (3.7%) compared with eyes that had prior conjunctival incisional surgery (1.3%), although this difference was statistically insignificant.

In conclusion, these data suggest that the risk of late-onset focal bleb leakage increases following trabeculotomy with adjunct mitomycin C therapy and occurs in as much as 6% of eyes. Localized, thin-walled blebs develop leaks more frequently than diffuse blebs with thicker walls. As such, late leakage after combined cataract and glaucoma surgery is infrequent.

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