Use of Tissue Plasminogen Activator to Revive Blebs Following Intraocular Surgery

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Background: Tissue plasminogen activator (tPA) is a serine protease with thrombolytic-fibrinolytic activity. In the anterior segment of the eye, it has been used to lyse blood and fibrin clots immediately following trabeculectomy.

Objective: To review our experience using tPA to revive previously functional but newly failing blebs following secondary surgical procedures (cataract extraction or penetrating keratoplasty).

Methods: A retrospective medical record review of all eyes receiving tPA to revive a failing bleb after a later anterior segment surgery was performed. Blebs were functional for at least 9 months before tPA, 12.5 µg, was injected into the anterior chamber. Eyes had longer than 6 months of follow-up after tPA use.

Results: Six eyes that had undergone phacoemulsification and 1 that had undergone penetrating keratoplasty were identified. Before the secondary surgery, blebs had been in place for 20.4±9.3 months, with an intraocular pressure of 10.7±3.6 mm Hg. New bleb failure in these eyes was observed following phacoemulsification or penetrating keratoplasty between postoperative days 4 and 14, with the intraocular pressure increasing to 27.7±9.5 mm Hg. One day after tPA use, the intraocular pressure had decreased to 11.0±3.7 mm Hg (P=.002). In 5 of the 7 patients, the bleb height improved following tPA use. The final intraocular pressure was 10.7±3.6 mm Hg at a follow-up of 13.4±6.4 months. (All data are given as mean±SD.)

Conclusion: Tissue plasminogen activator can be a useful adjunct for reviving newly failing blebs after other anterior segment surgery.


Many patients with well-functioning blebs after trabeculectomy ultimately require other ocular surgery. For example, it has long been thought that filtering surgery may be cataractogenic. In addition, one recent study reported that virtually all phakic eyes following filtering surgery with mitomycin supplementation develop cataractous changes. Many of these eyes eventually need cataract extraction. Similarly, for various reasons, filtered eyes may undergo other surgery, such as penetrating keratoplasty (PKP).

Although modern phacoemulsification may be associated with a minimum of postoperative inflammation, bleb dysfunction in the early postoperative period secondary to excessive inflammation occasionally occurs. This is especially true if extensive pupil manipulation has been necessary or if there is a history of recurrent uveitis. Similarly, intraocular inflammation following corneal graft procedures can be associated with bleb failure.

Recombinant tissue plasminogen activator (tPA) is a serine protease with thrombolytic-fibrinolytic activity. It has been used extensively in the treatment of ischemic stroke and myocardial infarction. In addition, it has been used intraocularly since the late 1980s to treat various problems, including subretinal heme, postvitrectomy fibrin formation, anterior chamber fibrin formation following cataract surgery, and fibrin clots immediately after glaucoma surgery.

We reviewed our experience using tPA to revive previously well-established blebs that ceased to function as before in the immediate period following secondary intraocular surgery.

Results

Of 7 patients, 7 eyes received a total of 7 injections of 12.5 µg of tPA (Table 1). Each eye had an established well-functioning bleb in place from an earlier trabeculectomy, which was done 20.4±9.3 months before the secondary surgery. The
PATIENTS AND METHODS

A retrospective medical record review of successfully filtered eyes receiving intracameral tPA following secondary intraocular surgery was conducted. In 7 patients, 7 eyes were identified. All eyes had at least 6 months of follow-up after the tPA injection.

The age of the patients ranged from 21 to 77 years. Five were white, and 2 were black; 4 were women, and 3 were men. Each eye had a history of a well-functioning filter for at least 9 months before secondary surgery. The initial diagnosis was primary open-angle glaucoma (n=3), low-tension glaucoma (n=1), uveitic glaucoma (n=1), Rieger anomaly (n=1), or juvenile glaucoma (n=1). Of the 7 eyes, 5 had undergone trabeculectomy with mitomycin and 2 with fluorouracil supplementation.

The secondary surgery in 6 of the 7 eyes was clear corneal phacoemulsification with intraocular lens implantation. Of these 6 eyes, 5 required intraoperative pupil manipulation (microspinhceterotomies and/or pupil stretching) during phacoemulsification. All of these eyes received foldable intraocular lenses (AMO S140; Allergan Inc, Irvine, Calif). The secondary procedure in 1 eye was a combined PKP, cataract extraction, and intraocular lens implantation. Care was taken at the conclusion of each secondary surgery to remove as much viscoelastic as possible from within the eyes. All phacoemulsification procedures were done by one of us (M.F.S. or J.W.D.).

Tissue plasminogen activator had been prepared previously by the hospital pharmacy staff. A 50-mg vial of lyophilized recombinant tPA (Activase; Genentech, Inc, San Francisco, Calif) (hospital cost, $1079) had been reconstituted and divided, under sterile conditions, into 100 separate portions, each 500 µg/mL. These portions had been stored in the hospital pharmacy at −20°C. Before use, 1 aliquot was thawed and further diluted with sterile balanced salt solution to a final concentration of 10 µg/0.1 mL.

Eyes that were injected with tPA were all in the immediate postoperative period (≤2 weeks after the secondary surgery). New bleb dysfunction was distinguished by new-onset bleb flattening and a substantial increase in intraocular pressure (IOP). After obtaining appropriate informed consent, eyes received topical tetracaine and dilute iodine. An eyelid speculum was inserted, and the patient was placed at the slitlamp. Then, 12.5 µg (0.125 mL) of tPA was injected into the anterior chamber with a 30-g cannula, through the preexisting paracentesis (6 eyes) or the PKP incision (1 eye). Some aqueous humor was allowed to egress through the injection site while the tPA was instilled.

All eyes were examined the next day and as necessary thereafter, with attention to Snellen vision, IOP, and bleb height. Eyes were also carefully inspected for the presence of any hemorrhage or change in corneal condition. Topical ocular corticosteroid therapy was increased in all patients for several weeks following tPA injection. All data are given as mean±SD.

Intracameral tPA has been used for more than a decade to treat various intraocular problems. Its use in glaucomatous eyes, to our knowledge, has previously been limited to the immediate postoperative period following trabeculectomy (or less commonly, glaucoma drainage implant surgery). Based on our experience, new trabeculectomy dysfunction following secondary intraocular surgery can be another indication for intracameral tPA administration.
In the past, tPA has been administered to directly treat visualized intraocular blood or fibrin. In our review, only 1 of 7 eyes had a gross fibrin response in the anterior chamber before tPA administration. All eyes, however, exhibited a significant inflammatory response despite the administration of high-dose preoperative and postoperative topical corticosteroids. Thus, although no gross sclerostomy blockage by fibrin was discernible, we hypothesized that there could be nonvisualizable fibrin blockage to aqueous humor outflow across the bleb. Previously, all blebs were highly functional, and no other cause for new-onset dysfunction was appreciable. We believe that remnant intraocular viscoelastic was not the cause of these cases of new bleb dysfunction, because none was visualized and one would expect dissipation of any viscoelastic before these problems developed (postoperative days 4-14). The significant decrease in IOP 1 day following tPA injection \((P = .002)\) supports the hypothesis that bleb dysfunction was caused, at least in part, by inflammation and fibrin deposition.

No major complications from tPA use occurred in this small series. Others have reported hyphema,10,11 band keratopathy,8,12 irreversible superficial corneal clouding,13 and even vitreous hemorrhage (after repeated tPA injections).14 These complications have been associated with higher single (ie, 25 µg) and/or multiple doses of intracameral tPA. It is not surprising that no bleeding was seen in this series, since a single lower dose of tPA was given following (relatively) bloodless cataract or corneal graft surgery.

Tissue plasminogen activator, as prepared in aliquots by a pharmacy, is not prohibitively expensive. A single 50-mg vial costs $1079. We have our pharmacy prepare 100 aliquots from a vial. Patients are charged approximately $25 for an aliquot. In that drug precipitation following frozen storage of aliquots with a tPA concentration of less than 20 µg/0.1 mL has been reported,15 we find storage of 50-µg/0.1 mL aliquots safe and easily dilutable following thawing.

Alternative interventions for new-onset bleb dysfunction following later surgical procedures include needle revision of the bleb16 and ocular massage. A major risk with needle revision of a bleb is inadvertent deroofing of the bleb, with a subsequent bleb leak and overdrainage, which in turn may require additional surgery. Other risks include suprachoroidal hemorrhage and hyphaema. In this series, needle revision of the bleb was attempted in patient 4, several weeks after the tPA injection failed to “revive” the bleb; it also was unsuccessful. Ocular massage was not attempted in any of these eyes, as they had all recently undergone clear corneal phacoemulsification or PKP. A newer option that could be con-

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Patient No./Race/ Age, y/Sex</th>
<th>Initial DX</th>
<th>Drug Used During the Initial Surgery†</th>
<th>Time Until the Secondary Procedure, mo</th>
<th>Preoperative‡</th>
<th>Secondary Surgery</th>
<th>MAX Postoperative (Days 4-14)</th>
<th>After tPA Administration</th>
<th>Final</th>
<th>Follow-up, mo</th>
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<tr>
<td>1/W/77/M</td>
<td>POAG</td>
<td>Fluorouracil</td>
<td>24</td>
<td>20/60 10</td>
<td>PHACO</td>
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<td>2/B/60/F</td>
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<td>Mitomycin</td>
<td>36</td>
<td>20/100 16</td>
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<td>Mitomycin</td>
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<td>20/200 5</td>
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<td>14</td>
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<tr>
<td>4/W/48/F</td>
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<td>8</td>
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</table>

*DX indicates diagnosis; IOP, intraocular pressure; VA, visual acuity; MAX, maximum; tPA, tissue plasminogen activator; POAG, primary open-angle glaucoma; PHACO, phacoemulsification; GL, glaucoma; PKP, penetrating keratoplasty; and LTG, low-tension glaucoma.
†The initial surgical procedure was trabeculectomy for all patients.
‡There was no preoperative medication for any patient.

**Table 2. Intraocular Pressure (IOP) Summary**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Baseline IOP, mm Hg</th>
<th>No. of GL MEDS</th>
<th>After TRAB IOP, mm Hg</th>
<th>Follow-up IOP, mm Hg</th>
<th>No. of GL MEDS</th>
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</table>

*GL MEDS indicates glaucoma medications; TRAB, trabeculectomy; tPA, tissue plasminogen activator; POD, postoperative day; and MAX, maximum.
sidered in such cases is Nd:YAG transconjunctival laser revision. In that we did not observe any scar tissue within these blebs, this laser therapy was not used.

In the past in filtered eyes, cataract extraction has been associated with decreased aqueous humor outflow and bleb failure. Kasahara et al described simultaneous corneal incision phacoemulsification and internal revision of the filtering bleb in 19 eyes, with bleb preservation in 89.4% of the eyes and no postoperative change in IOP. In our experience, phacoemulsification can be far less traumatic to an eye compared with extracapsular large-incision surgery. In fact, by maximizing perioperative anti-inflammatory eyedrop use and carefully removing all viscoelastic at case conclusion, phacoemulsification in patients with functioning blebs has been associated with no significant IOP elevation 73% of the time and with only a mild medically controllable elevation in IOP another 16.7% of the time. Therefore, we do not routinely internally revise functioning blebs at the time of phacoemulsification.

Limitations of this study include its retrospective nonrandomized nature and the relatively small number of patients. It is possible that previous bleb function would have resumed in these eyes had nothing been done. However, as already noted, a significant percentage of filtered eyes lose an important degree of bleb function following phacoemulsification. This study points out an additional reasonable option for therapeutic consideration. With a mean follow-up of more than 1 year, no tPA-associated complications have arisen in any of the treated eyes, and the IOP outcome is good. Furthermore, tPA use as described is not unacceptably costly or time-consuming. Future prospective randomized studies will provide important supplementary data.

Accepted for publication December 21, 2000.

This study was supported in part by a departmental grant from Research to Prevent Blindness Inc, New York, NY.

Presented in part at the Association for Research in Vision and Ophthalmology Meeting, Fort Lauderdale, Fla, May 2, 2000.

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REFERENCES