Treatment of Submacular Hemorrhage With Low-Dose Intravitreal Tissue Plasminogen Activator Injection and Pneumatic Displacement
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Objective: To investigate the safety and efficacy of low-dose intravitreal tissue plasminogen activator (tPA) and an expansile gas bubble in displacing submacular hemorrhage in patients with age-related macular degeneration (ARMD).

Patients and Methods: We reviewed retrospectively the medical records of 14 consecutive patients with ARMD from 1 academic center who received low-dose intravitreal tPA (18-50 µg) and expansile gas (0.3-0.4 mL of perfluoropropane) for thrombolysis and displacement of submacular hemorrhage. After the procedure, patients maintained face-down positioning for 1 to 3 days.

Main Outcome Measures: Displacement of blood from the fovea, early and final visual acuity, and toxicity of tPA.

Results: Submacular blood was completely displaced from the fovea in 10 (71%) of the 14 patients and partially displaced in 3 (21%). In 1 patient, no displacement occurred. Early (<2 months) postoperative visual acuity improved by 2 or more lines in 8 patients (57%). With a mean follow-up of 7.7 months, 2 (15%) of 13 patients maintained 2 or more lines of improvement and 69% (9 patients) maintained preoperative visual acuity. No clinical evidence of retinal toxicity was seen at this low-dose of tPA.

Conclusions: Doses of intravitreal tPA ranging from 18 to 50 µg and an expansile gas bubble are safe and effective in displacing submacular hemorrhage in patients with ARMD. Final visual acuity was limited by the underlying presence of end-stage ARMD.


The visual outcome in patients with age-related macular degeneration (ARMD) and a submacular hemorrhage is typically poor. In patients with submacular hemorrhage, the prognosis is worse when the blood cover is thick, covers a large area of the macula, and is accompanied by a choroidal neovascular membrane.

In 1996, Heriot presented a new procedure to lyse and displace submacular blood without intraocular surgery by injecting intravitreal tissue plasminogen activator (tPA) and a bubble of long-acting expansile gas into the vitreous cavity. Heriot’s technique uses 100 µg of intravitreal tPA to liquify the submacular blood clot and an intravitreal gas bubble combined with face-down positioning to directly compress the macula and displace the submacular blood inferiorly.

Investigators have reported success in displacement of submacular blood using this procedure in patients with ARMD, macroneurysms, and trauma. However, there is a question of retinal toxicity from the tPA at a dose of 100 µg. We have modified Heriot’s technique by using a lower dose of intravitreal tPA to determine whether this method is safe and effective in the management of submacular hemorrhage.

RESULTS
Fourteen eyes of 14 patients (7 men and 7 women) with ARMD and submacular hemorrhage underwent intravitreal injection of low-dose tPA and long-acting expansile gas bubble (Table). Mean follow-up of patients was 7.7 months (range, 1-15 months). One patient was lost to follow-up 1 month after treatment. The age of the patients ranged from 71 to 97 years (mean age, 81 years), and the duration of symptoms from submacular hemorrhage ranged from 1 to 21 days (mean, 9 days). The size of the hemorrhage ranged from 3.5 to 44 disc areas (mean, 16 disc areas) and, in all patients, the hemorrhage was thick (defined as elevation of the retina on stereoscopic clinical examination).

The procedure resulted in complete displacement of blood from the center of
PATIENTS AND METHODS

We reviewed the medical and photographic records of 14 consecutive patients at the University of Wisconsin, Madison, who underwent intravitreal injection of low-dose tPA and long-acting expansile gas for thrombolysis and displacement of submacular hemorrhage between February 1997 and December 1998. Four retinal specialists (B.A.B., S.R.C., T.W.O., and T.S.S.) performed the 14 procedures. Inclusion criteria consisted of symptomatic submacular hemorrhage for less than 3 weeks, thick blood under the fovea resulting in retinal elevation, and a hemorrhage of at least 3 disc areas. Patients with thick blood beneath the retinal pigment epithelium were not excluded in this series. Although the majority of eligible patients elected to undergo this experimental therapy, the number of patients who refused treatment during this time is not known.

Each patient underwent complete ophthalmologic examination. Visual acuity was obtained using the patients' current spectacle correction and pinhole. Visual acuity testing was not standardized and patients were not refracted. Visual acuity less than 20/400 on the Snellen chart was categorized by the distance at which a patient was able to count fingers (eg, 1/200, 2/200, 3/200). For data analysis, these acuities were grouped as “count fingers.” For 2 patients, the final visual acuity was obtained via a telephone call to the referring ophthalmologists. Stereoscopic color fundus photographs were taken of all patients at initial presentation except for 1 patient who presented on a weekend.

Fluorescein angiography was performed on 4 patients (29%) and fluorescein angiography and indocyanine green angiography were performed on 5 patients (36%). None of the initial angiograms demonstrated choroidal neovascular membranes that were treatable by conventional photocoagulation.

After obtaining informed consent, the procedure was performed in the outpatient clinic under retrobulbar anesthesia, using sterile technique. This was followed by an anterior chamber paracentesis and a pars plana injection of low-dose tPA (18-50 µg in a concentration of 20-30 µg/0.1 mL) into the midvitreous cavity. Pure perfluoropropane (0.1-0.3 mL) was injected into the midvitreous using the same technique. Each patient began prone positioning within several hours of the procedure and maintained positioning for 24 to 72 hours as directed by the treating ophthalmologist. Follow-up care was determined on an individual basis by the treating ophthalmologist.

The efficacy of the procedure was assessed by the following outcome measures: (1) degree of subfoveal blood displacement, (2) best early posttreatment (<2 months) visual acuity, (3) late posttreatment (>3 months) visual acuity, and (4) absence of retinal toxicity. Two of us (B.A.H. and B.A.B.) assessed the degree of blood displacement from the fovea by comparing stereoscopic color fundus photographs taken prior to and 1 to 2 weeks after the procedure. The degree of blood displacement from the fovea was graded as complete, partial, or no displacement. Complete displacement was defined as more than 90% of blood cleared from the subfoveal space, partial displacement as 20% to 90% clearance of blood, and no displacement as less than 20% displacement.

Data of Patients With Age-Related Macular Degeneration*

<table>
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<th>Patient No.</th>
<th>Age, y/ Sex/Eye</th>
<th>Follow-up, mo</th>
<th>Duration of Symptoms, d</th>
<th>Areas of SMH</th>
<th>IPA Dose, µg</th>
<th>Pretreatment VA</th>
<th>Early Posttreatment VA (0-2 mo)</th>
<th>Late Posttreatment VA (&gt;3 mo)</th>
<th>Displacement of SMH</th>
<th>Final Macular Status</th>
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*SMH indicates submacular hemorrhage; IPA, tissue plasminogen activator; VA, visual acuity; FVPED, fibrovascular pigment epithelial detachment; PEDs, pigment epithelial detachments; and CNV, choroidal neovascularization.

the macula in 10 (71%) of 14 patients (Figure 1). Partial displacement of the blood occurred in 21% (3 patients) and no displacement of the blood occurred in 7% (1 patient), following the procedure.

Immediately prior to treatment, the visual acuity of all 14 patients with submacular hemorrhage ranged from 20/80 to 1/200. In 11 patients, the visual acuity before the hemorrhage ranged from 20/25 to 20/80. The visual acuity of the remaining 3 patients prior to the hemorrhage is not known. All patients had signs of ARMD in the fellow eye, consisting of drusen, geographic atrophy, retinal pigment epithelial changes, or choroidal neovascularization. Six patients had lost central vision (<20/200) in the other eye due to exudative macular degeneration.
In the first 2 months of follow-up, 8 (57%) of 14 patients gained 2 or more lines of visual acuity while 5 (36%) did not have any change in visual acuity. One patient (7%) lost 2 or more lines of visual acuity. With long-term follow-up, 2 (15%) of 13 patients maintained the improvement of 2 or more lines in visual acuity, 9 patients (69%) maintained their preoperative visual acuity, and 2 patients (15%) had a decline of visual acuity of more than 2 lines. One patient did not return after the 1-month visit. Visual loss in these patients was due to chronic subfoveal choroidal neovascularization and subretinal fibrosis.

Displacement of the blood uncovered the underlying macular pathology in 13 (93%) of 14 patients. Of the 14 patients, 12 had a choroidal neovascular membrane. Ten of these patients had a subfoveal fibrovascular pigment epithelial detachment (Figure 2 and Figure 3), 1 patient had a juxtapfoveal classic choroidal neovascular membrane, 1 had a poorly demarcated subfoveal occult choroidal neovascular membrane, and 1 had multiple pigment epithelial detachments. The remaining patient had geographic atrophy, which was not identified early in the posttreatment period because there was no displacement of blood. Posttreatment fluorescein and indocyanine green angiograms were performed on 7 patients (50%) in an attempt to identify a treatable lesion. None of these patients had lesions that were deemed treatable with conventional laser.

There were no complications during the procedure itself. One patient had corneal edema on the first day after the procedure, presumably from a transient rise in intraocular pressure. One patient with a massive subretinal hemorrhage had complete displacement of the blood from the center of the macula yet developed a vitreous hemorrhage 2 weeks later. The hemorrhage did not clear from the vitreous and the patient underwent pars plana vitrectomy. One patient had a posterior retinal tear within the superotemporal arcade and another patient had a rip in the retinal pigment epithelium, both of which occurred several days after the procedure. No patient had a recurrent hemorrhage in the postoperative period. There was no clinical evidence of retinal or retinal pigment epithelial toxicity from the tPA in any of the 14 patients.

Our results using low-dose tPA and an expansile gas bubble in patients with ARMD compare favorably with the visual acuity outcomes in 2 series using higher doses of tPA. In our series, 9 (64%) of 14 patients had a final visual acuity of 20/400 or better. Heriot9 reported that 3 (17%) of 18 patients with ARMD had a visual acuity of 20/200 or better while Hassan and colleagues10 report that 10 (71%) of 14 ARMD patients had a visual acuity of 20/400 or better. Although initial visual acuity improved in the majority of our patients, with long-term follow-up their visual acuity stabilized at their preoperative level.

The natural history of submacular hemorrhage in patients with ARMD carries a worse prognosis than other conditions such as trauma or macroaneurysm. However, retrospective reports on the visual outcome in untreated eyes with ARMD and submacular hemorrhage are variable. Bennett and colleagues1 reported only 3 (25%) of 12 ARMD patients had a final visual acuity of 20/400 or better while Berrocal and coworkers3 reported that 18 (90%) of the 20 ARMD patients had a visual acuity of 20/400 or better.

Animal studies have shown that the most immediate damage from subretinal blood may be due to the shearing of photoreceptors during clot retraction. Damage to the retina also occurs when thick subretinal blood forms a mechanical barrier preventing metabolic exchange between the retina and retinal pigment epithelium and by iron toxicity.8,9 The destructive effect of subretinal blood has prompted investigation into new methods of removing submacular blood to minimize retinal damage and to improve visual prognosis. In theory, removal of the blood should be timely to decrease the photoreceptor damage caused by clot retraction and to uncover any choroidal neovascularization that may be treatable by photocoagulation. Pars plana vitrectomy has been performed in patients with recent submacular hemorrhages to internally evacuate subretinal blood.10 Subretinal tPA has been used as a surgical adjunct during vitrectomy to dissolve submacular clots, potentially minimizing photoreceptor cell shearing.11,12
Two studies of ARMD patients undergoing submacular surgery and intraoperative tPA reported an initial postoperative improvement in visual acuity. However, at 6-month follow-up, Lim and colleagues reported a deterioration in visual acuity due to choroidal neovascularization, subretinal fibrosis, and retinal pigment epithelial atrophy. Only 5 (31%) of 16 eyes with ARMD had a final visual acuity of 20/400 or better. Lewis reported a visual outcome of 20/400 or better in 11 (44%) of 25 patients at greater than 6-month follow-up. In both series, the overall rate of complications was 20% to 30% and included rhegmatogenous retinal detachment, proliferative vitreoretinopathy, recurrent subretinal hemorrhage, inadvertent retinectomy, cataract, and macular hole. Based on these small numbers, the final visual acuity in our series is similar to those patients undergoing submacular surgery.

The limited success in final visual outcome and the risk of complications from surgical intervention has directed efforts toward a less invasive treatment for submacular hemorrhage. Our experience confirms that the minimally invasive technique developed by Heriot using intravitreal tPA and a gas bubble combined with face-down positioning is effective at displacing thick subfoveal blood. Using tPA and a gas bubble, displacement of blood from the center of the macula occurred in 19 (95%) of 20 patients in Heriot’s series and 100% (15 of 15 patients) in the series of Hassan et al. In our series, we had no serious complications such as endophthalmitis, retinal detachment, or proliferative vitreoretinopathy.

Because of our concern for retinal toxicity, we chose to treat patients with a significantly lower dose of tPA (18-50 µg) compared with that used by Heriot and Hassan et al (50-100 µg). In rabbit eyes, 100 µg of tPA treated with expansile gas can cause toxic retinal damage, including retinal holes, bullous retinal detachment, attenuation of retinal blood vessels, and marked early reduction in B-wave amplitude on the electroretinogram. In rabbits receiving 25 to 50 µg of tPA, there were no toxic retinal changes visualized on indirect ophthalmoscopy, electroretinogram, or light microscopy. Although the human eye has a larger vitreous volume than the rabbit.

Figure 2. Patient 9. An 85-year-old woman with a thick submacular hemorrhage in the right eye of 21 days’ duration. A, Pretreatment photograph shows subretinal and subpigment epithelial blood (notice the drusen overlying the blood centrally). Visual acuity was 20/100. B, Nine days after injection with tPA and perfluoropropane the subretinal blood has been completely displaced. The central orange pigment represents persistent subretinal pigment epithelial blood within the fibrovascular pigment epithelial detachment. Visual acuity improved to 20/80 at this time and declined to 20/400 after 15-month follow-up.

Figure 3. Patient 14. A 76-year-old man had 8 days of decreased vision in the right eye. A, Pretreatment photographs show extensive submacular hemorrhage. Visual acuity was 1/200. B, Two weeks following tPA and perfluoropropane injection, the blood under the fovea has cleared revealing a large subfoveal fibrovascular pigment epithelial detachment. Visual acuity improved to 20/150. Final visual acuity decreased to 1/200 after 7-month follow-up.
eye, a patient treated with 100 µg of tPA for submacular hemorrhage demonstrated severe pigmentary changes with marked visual loss (H. Gilbert, MD, unpublished data presented at the Vitreous Society, 1997). With this lower dose of tPA, we did not observe any retinal pigmentary changes or unexplained visual loss in our patients. However, we did not perform electroretinograms on our patients to measure retinal toxicity.

Despite reports of toxicity in animals and humans, the diffusion of tPA from the vitreous through the neurosensory retina is not completely understood. Kamei and colleagues reported that intravitreal tPA labeled with fluorescein isothiocyanate did not diffuse into the subretinal space in the rabbit. However, albumin (68 kd), a protein with a molecular weight similar to tPA (70 kd) has been shown to diffuse across the retina within 1 hour after intravitreal injection in rabbit eyes. Clot lysis of submacular hemorrhage in rabbits and pigs was visualized 24 hours after injection of intravitreal tPA while saline-treated eyes showed no change in clot size. In humans, Kimura et al treated 6 patients who had acute (2-4 days) subretinal hemorrhages with intravitreal tPA 12 to 36 hours before surgery and noted liquefied blood at the time of surgery.

Investigators have recently attempted pneumatic displacement of submacular hemorrhage without tPA. Ohji and colleagues reported a series of 5 patients treated with pure perfluoropropane gas and prone positioning 4 to 18 days after the onset of hemorrhage. Blood displacement from the fovea occurred partially or completely in all 5 patients. Ohji and colleagues speculate that solid blood clots that present more than 1 week may not be displaced with gas compression alone. In our series, we cannot separate the effect of the tPA from the gas bubble in the displacement of submacular hemorrhage. As a result, there is no direct evidence that tPA is necessary for the success of the procedure.

In our series, there was no association between the duration of symptoms or the area of hemorrhage to the final visual outcome. Our retrospective series is small and did not have a control group or a standardized protocol for visual acuity measurement and follow-up care. A randomized clinical trial comparing similar eyes with and without treatment would help determine if this minimally invasive procedure is beneficial.

At this time, the presence of underlying occult subfoveal choroidal neovascularization (primarily fibrovascular pigment epithelial detachments) appears to be the most important contributing factor to the visual prognosis in patients with submacular hemorrhage. We have shown, however, that the displacement of submacular hemorrhage with intravitreal low-dose tPA and an expansile gas bubble is effective and safe. As new treatments for subfoveal choroidal new vessels are now becoming available, this minimally invasive technique may be useful in displacing the blood and uncovering previously untreated lesions.

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REFERENCES