AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Pneumatic Displacement of Submacular Hemorrhage with Subretinal Air and Tissue Plasminogen Activator

Initial United States Experience

Sumit Sharma, MD,[1,] Jaya B. Kumar, MD,[1,*] Judy E. Kim, MD,[2] John Thordsen, MD,[3] Pouya Dayani, MD,[4] Michael Ober, MD,[5] Tamer H. Mahmoud, MD, PhD[6]*

Purpose: To present the initial multicenter experience of using subretinal air injection in combination with tissue plasminogen activator (tPA) at the time of pars plana vitrectomy (PPV) to displace submacular hemorrhage (SMH).

Design: Retrospective, noncomparative, interventional case series.

Participants: Patients with SMH resulting from age-related macular degeneration or polypoidal choroidal vasculopathy.

Methods: Chart review of patients who underwent displacement of SMH with PPV, subretinal injection of air and tPA (125 mg/mL), partial fluid–air exchange with gas tamponade, and preoperative, intraoperative, or postoperative intravitreal injection of anti–vascular endothelial growth factor agent at 5 sites in the United States. None of the surgeons had prior experience with using subretinal air.

Main Outcome Measures: Frequency and extent of SMH displacement, preoperative and postoperative visual acuities and retinal thickness, and postoperative complications.

Results: Twenty-four eyes of 24 patients were included (11 men; mean age, 79.1 years) with a mean follow-up of 12.5 months (range, 3–28 months). At 3 months after surgery, complete displacement of SMH from the foveal center was achieved in 24 eyes (100%), displaced beyond the arcades in 75% and beyond the equator in 20%. Residual subretinal pigment epithelial hemorrhage was seen in 5 eyes (20.8%). Mean preoperative and postoperative visual acuity was 1.95 logarithm of the minimum angle of resolution (logMAR; Snellen equivalent, 20/1783) and 0.85 logMAR (Snellen equivalent, 20/141; $P < 0.0001$), respectively. Visual acuity improved in 23 eyes (95.8%) and was unchanged in 1 eye. Mean central retinal thickness improved from 463.7 μm before surgery to 311.3 μm at the final visit ($P = 0.026$).

Conclusions: This initial experience of injecting subretinal air at the time of tPA injection during PPV showed the technique to be effective, with high consistency to displace SMH away from the fovea and even out to the periphery, and resulted in improved VA and retinal thickness. Some cases of subretinal pigment epithelial hemorrhage also benefit from this technique. *Ophthalmology Retina 2017;■:1–7 © 2017 by the American Academy of Ophthalmology*

Large submacular hemorrhage (SMH) is a rare but devastating complication of choroidal neovascularization. Without treatment, large SMH may lead to severe and irreversible vision loss, and the degree of vision loss may continue to worsen over time.[1,2] The longer the hemorrhage is present in the subretinal space, the worse the visual prognosis.[3] Animal studies demonstrate that hemorrhage in the subretinal space results in severe damage to photoreceptors and the outer nuclear layer within 24 hours[4] and further degeneration of photoreceptors and retinal pigment epithelium (RPE) at 7 days.[5] Surgically removing subretinal clots requires a large retinotomy (approximately 310 μm), increasing the risk for retinal detachment and proliferative vitreoretinopathy.[6] Therefore, subretinal tissue plasminogen activator (tPA) has been used to liquefy the SMH and facilitate aspiration.[6]

Several surgical techniques have been proposed to displace SMH with variable success. Early reports used subretinal tPA and perfluorocarbon liquid to facilitate aspiration through a small retinotomy.[7,8] However, this technique has fallen out of favor because of dismal postoperative visual acuity (VA) and high rates of retinal detachment. A less invasive outpatient procedure of intravitreal tPA and expansile gas to displace SMH pneumatically was described[9] with initial encouraging results, but its usefulness was limited to small or thin SMH. The combination of pars plana vitrectomy (PPV), subretinal tPA, and pneumatic displacement of SMH was proposed with variable rates of

Published by Elsevier Inc.

http://dx.doi.org/10.1016/j.oret.2017.07.012
ISSN 2468-6530/17

success.[10,11] A recent comparative interventional case series with a large cohort of patients used PPV and subretinal tPA with postoperative intravitreal anti−vascular endothelial growth factor (VEGF), on the hypothesis that concurrent postoperative use of anti-VEGF may prevent regression of treatment effect.[12] Although this approach had promising results, the degree of displacement was limited in most cases. Currently, there is no consensus on the optimal management of SMH.

Injection of subretinal air in combination with subretinal tPA as a way to manage subretinal hemorrhage was described first by Martel and Mahmoud[13] and Yiu and Mahmoud.[14] This technique relies on the forces influencing SMH mobility as described by Martel and Mahmoud[13] and Stopa et al.[15] Addition of subretinal air enhances the buoyant force exerted on the hemorrhage and allows for more consistent and further displacement of hemorrhage from the macula. After the original report, interventional case series in Japan and India showed favorable outcomes, including further displacement of the hemorrhage, fewer postoperative complications, and earlier VA improvement.[16,17] We present the initial experience in the United States of PPV with subretinal tPA and subretinal air to enhance displacement of SMH.

Methods

After institutional review board and ethics committee approvals were obtained, we reviewed the medical records of 24 consecutive patients (24 eyes) with SMH from 5 sites operated by 1 surgeon at each site (JEK, JT, PD, MO, THM) from February 1, 2013, through December 30, 2015. Submacular hemorrhage was defined as a subretinal hemorrhage involving the foveal center amenable to surgical displacement and thick enough to require surgical intervention according to the treating physician. Patients' underlying diagnoses were recorded. All patients underwent PPV with induction of a posterior vitreous detachment, if necessary, followed by subretinal injection of tPA, filtered air, and in some cases, anti-VEGF. Although all surgeons had experience with using subretinal tPA, none of the surgeons had previous experience with injecting subretinal air for displacement of SMH.

To prepare the subretinal injection, 0.2 mL filtered air was drawn in a 1-mL tuberculin syringe followed by 0.4 mL tPA at a concentration of 12.5 μm/0.1 mL (total, 50 μm),[18,19] for a total volume of 0.6 mL.[13] Some patients received an additional 0.1 mL bevacizumab (2.5 mg/0.1 mL) in the same syringe. The syringe then was connected to an extendable 41-gauge subretinal needle on a 23-gauge cannula and held pointing down such that the filtered air rose to the top away from the needle end. The subretinal combination then was injected in the SMH into the subretinal space at a safe distance away from the fovea. Next, a partial fluid−air exchange was performed followed by exchange with a nonexpansile gas, either sulfur hexafluoride (20% SF_6) or perfluoropropane (14% C_3F_8), or left with filtered air, to fill approximately 50% of vitreous cavity, with the goal of preventing superior tracking of the subretinal hemorrhage and subretinal air. After surgery, the patient was positioned upright.

Medical records were reviewed for VA at baseline and postoperative visits, gender, age at presentation, anticoagulation status and indication, duration of hemorrhage before surgical intervention, type of gas, preoperative and postoperative anti-VEGF injections, morphologic features of hemorrhage on OCT at baseline and follow-up, postoperative complications and management, and overall postoperative management (which varied based on the discretion of the managing physician). Visual acuities were converted to the logarithm of the minimum angle of resolution (logMAR) scale for statistical analysis. Visual acuities of counting fingers were converted to 2.0 logMAR (Snellen equivalent, 20/2000) and those of hand movements were converted to 3.0 logMAR (Snellen equivalent, 20/20 000), as previously described.[20]

The preoperative hemorrhage was graded on fundus photographs as small (within the arcades), large (reaches the arcades), extensive (beyond the arcades), or massive (beyond the equator, involving 2 retinal quadrants, or both). The degree of blood displacement was determined using fundus photographs and was graded as within the macula, beyond the arcades, or beyond the equator. All patients were followed up for a minimum of 3 months. All numerical comparisons were performed using the Wilcoxon signed-rank test. Stepwise multivariate linear regression was performed to determine preoperative factors that were best predictive of postoperative VA. All data were analyzed using JMP software version 12.0.1 (SAS Institute, Inc., Cary, NC).

Results

A total of 24 eyes of 24 patients (13 women, 11 men) were included in the study. The mean age was 79.1 years (range, 62−92 years). Patients were followed up for an average of 12.5 months (range, 3−28 months). Twenty patients had age-related macular degeneration (83%) and 4 had polypoidal choroidal vasculopathy (17%) as the underlying cause of SMH. Thirteen patients (54%) were receiving anticoagulation medication; 7 were taking 81 mg aspirin (54%), 3 were taking warfarin (23%), 1 was taking clopidogrel (7.7%), 1 was taking baby aspirin and clopidogrel (7.7%), and 1 was taking full-dose aspirin (7.7%). The reasons for anticoagulation were atrial fibrillation in 1 patient, history of stroke in 3 patients, and as a preventative in 9 patients.

The average duration from onset of symptoms to surgery was 11.3 days (range, 1−59 days; median, 9 days). Based on review of OCT images, it was believed that SMH was subretinal in 5 patients (20.8%), sub-RPE in 2 patients (8.3%), and both subretinal and sub-RPE in 17 patients (70.8%). The hemorrhages were defined as thin (<500 μm) in 7 patients (29.2%) and thick (>500 μm) in 17 patients (70.8%). The hemorrhages were described as small (does not reach arcades) in 6 patients (25%), large (extending to the arcades) in 2 patients (8.3%), extensive (extending past the arcades) in 9 patients (37.5%), and massive (extending to 2 quadrants, past the equator, or both) in 7 patients (29.2%).

All procedures included PPV with subretinal injection of tPA and air into the subretinal space. Seventeen eyes (70.8%) also underwent subretinal injection of bevacizumab, 2 eyes (8.3%) underwent intravitreal injection of bevacizumab as part of the surgical procedure, 4 eyes (16.7%) underwent preoperative injection of bevacizumab, and 1 eye did not receive bevacizumab as part of the treatment or surgery. Perfluoropropane (C_3F_8) gas was used in 1 eye (4.2%), sulfur hexafluoride (SF_6) gas was used in 14 eyes (58.3%), and air was used in 9 eyes (37.5%). No intraoperative complications were detected except in 1 patient, in whom a macular hole was seen at the time of subretinal injection.

Complete subfoveal displacement of thick subretinal hemorrhage was noted in 21 eyes (87.5%) at 1 week after surgery and could not be determined accurately in 3 eyes (12.5%) because of postoperative vitreous hemorrhage. At 3 months after surgery, there was complete displacement of thick subretinal hemorrhage