Intravitreal Versus Subretinal Tissue Plasminogen Activator Injection for Submacular Hemorrhage

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BACKGROUND AND OBJECTIVE: The objective of this study was to compare visual acuity outcomes between the following procedures used to treat submacular hemorrhages: pneumatic displacement followed by intravitreal tissue plasminogen activator (tPA) if needed (pneumatic ± tPA) and pars plana vitrectomy (PPV) with subretinal tPA (PPV + tPA).

PATIENTS AND METHODS: This is a retrospective chart review of submacular hemorrhages treated with either pneumatic ± tPA or PPV + tPA.

RESULTS: Eighteen patients had pneumatic ± tPA, and 14 patients had PPV + tPA. The percentage of patients achieving three lines or greater of vision improvement 1 year postoperatively was 46% and 18% in these groups, respectively ($P = .194$).

CONCLUSION: The difference in visual acuity was not statistically significant; however, the lack of a statistical difference is important as pneumatic ± tPA is a less-invasive, less costly procedure that can be done in a clinical setting.

INTRODUCTION

Submacular hemorrhages can have devastating consequences for central vision, and they can stem from various causes, including age-related macular degeneration (AMD) and retinal artery macroaneurysms (RAMs). The goal in managing these patients is to displace the hemorrhage away from the central macula. Many techniques for displacement have been used, and several of them involve tissue plasminogen activator (tPA). tPA is a protease that functions by converting plasminogen to plasmin, which will then break fibrin into fibrin degradation products and help liquefy a blood clot. The hemorrhage can then be displaced with a gas or air bubble. The methods to repair submacular hemorrhage vary and include observation, intravitreal tPA injection with or without pneumatic displacement, pars plana vitrectomy (PPV) with intravitreal or subretinal tPA injection with or without subretinal air injection, and PPV with extensive submacular surgery.\textsuperscript{1-29} Many of the studies evaluating these methods focus on displacement of hemorrhage rather than visual acuity and have follow-up periods of shorter than 1 year.

We believe that long-term visual acuity instead of physical displacement of the hemorrhage is a more meaningful assessment of these techniques and therefore undertook the current study. We have also observed that with treatment, many patients either have relatively little improvement or have a very signifi-

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Originally submitted June 23, 2016. Revision received October 1, 2016. Accepted for publication October 10, 2016.

Previously presented as a poster at the annual American Society of Retina Specialists meeting in Toronto, Ontario, Canada, on August 24–25, 2013.

Supported in part by an unrestricted grant from Research to Prevent Blindness, New York, to the Department of Ophthalmology & Visual Sciences, University of Utah. Research to Prevent Blindness had no role in study design, collection, analysis, and interpretation of data, or writing the report.

The authors report no relevant financial disclosures.

The authors would like to acknowledge Molly McFadden, MS, for her help with the statistical analysis performed for the project.

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doi: 10.3928/23258160-20161219-04
cant improvement. For that reason, we chose to make the number of patients with visually significant improvement rather than the average change in visual acuity our primary outcome.

At our institution, one of the vitreoretinal surgeons performs pneumatic displacements with possible intravitreal tPA injection exclusively, whereas another vitreoretinal surgeon performs PPV with subretinal tPA injection exclusively. Therefore, we feel that a retrospective chart review comparing the visual outcomes of patients with submacular hemorrhage, minimum follow-up of 1 year, and treatment by these two physicians who have the same referral base would provide valuable comparative data on the efficacy of these two approaches.

**PATIENTS AND METHODS**

This study was an institutional review board-approved, single-site, retrospective chart review. Selection criteria included submacular hemorrhage less than 2 weeks old. Exclusion criteria included any other ocular abnormalities that would affect vision other than mild cataract. Charts from 2002 to 2015 of two retina faculty members were reviewed. One method to identify charts was to search the pharmacy record for any use of tPA. A second method was to search for the CPT code for pneumatic displacement (67025). Injection of tPA into the eye is considered an off-label use of this product.

The pneumatic ± tPA group included patients who had submacular hemorrhage (Figures 1 and 2) who were treated with 0.3 mL of pure intravitreal perfluoropropane (C3F8) injection followed by an immediate anterior chamber paracentesis. Then, a 0.1 mL intravitreal tPA (25 µg / 0.1 mL) injection was performed 1 day to 3 days later in clinic if full displacement of the hemorrhage had not occurred; if displacement did occur, no tPA was injected. Patients were instructed to remain face-down during the interval between the C3F8 injection and the tPA injection. The patients who received intravitreal tPA could face forward for a few hours and then resumed face-down positioning for 2 to 3 more days. An experienced vitreoretinal surgeon, Surgeon A, performed all procedures in the pneumatic ± tPA group.

The PPV + tPA group consisted of patients with submacular hemorrhage who were treated with a 25-gauge three-port PPV combined with 0.1mL to 0.3 mL of subretinal tPA injected at a concentration of 12.5 µg / 0.1 mL with a soft-tipped 39-gauge cannula.
followed by a partial air-fluid exchange. The patients remained face-down for several days after their surgery to help displace the hemorrhage. An experienced vitreoretinal surgeon, Surgeon B, performed all procedures in the PPV + tPA group. It should be noted that the referral base for Surgeon A and Surgeon B is the same.

Patient age, sex, preoperative visual acuity, underlying etiology leading to the submacular hemorrhage, and use of blood thinners including aspirin and warfarin were recorded. Patients’ Snellen visual acuities were also recorded at postoperative months 1, 6, and 12. If a patient did not have a visit at any time point, that visit was excluded from analysis. The primary outcome was the percentage of patients who improved by at least three lines on the Snellen Visual Acuity Chart when compared to their preoperative visual acuity. There was no planned standardization for technicians to use for patients with visual acuity worse than 20/400, so any visual acuity worse than 20/400 was considered the same line.

Statistical analysis for the primary outcome of the study was performed using generalized estimating equations to allow repeated measures in logistic regression with the categorical outcome of improvement of at least three lines on the software Proc Gen-

Figure 2. Optical coherence tomography (OCT) imaging from the same patient as in Figure 1. Again, this patient is from the pneumatic ± tissue plasminogen activator (tPA) group. It should be noted that there is no OCT from the clinic visit when the patient received intravitreal tPA. (A) Presentation. Visual acuity is 20/400. B) One month post-pneumatic and tPA. Visual acuity is 20/200. C) Three months post-pneumatic and tPA. Visual acuity is 20/40. (D) Twelve months post-pneumatic and tPA. Visual acuity is 20/80.
mod in SAS version 9.4 (Cary, NC). Covariate adjustment for baseline visual acuity was included in all analyses.

RESULTS

Eighteen patients were in the pneumatic ± tPA group, and 14 patients were in the PPV + tPA group. The average age in the pneumatic ± tPA group was 74.7 years (standard deviation [SD]: 14.9 years), whereas in the PPV + tPA group it was 76 (SD: 6.2 years).

Sixteen out of 18 patients in the pneumatic ± tPA group had AMD. One patient had a RAM, and one had pathologic myopia. All procedures in this group were performed by Surgeon A. Ten out of 18 patients were using a blood thinner. All patients had an intravitreal anti-vascular endothelial growth factor (anti-VEGF injection) within 1 week postoperatively of their procedure. Nine patients had pre-operative visual acuities of worse than 20/400, and three had visual acuities of 20/400. The remaining six had visual acuities between 20/125 and 20/300. Two patients had displacement of their hemorrhages with C3F8 alone.

In the PPV + tPA group, 12 patients had AMD, two had RAMs, and all had their surgeries performed by Surgeon B; nine of 14 patients were using a blood thinner. Within 1 month after their surgery, five of 12 patients with AMD in this group received intravitreal anti-VEGF injections. Three of the remaining seven patients received PDT within 3 months after their surgery. Eleven patients in the PPV + tPA group had preoperative visual acuities of worse than 20/400 and three patients were 20/400. The patients with the RAMs had preoperative visual acuities of count fingers.

The primary outcome of the study was the percentage of patients in each group with an improvement in visual acuity of at least three lines (Figure 3). With regards to the pneumatic ± tPA and the PPV + tPA groups, respectively, at postoperative month 1, 37% (six of 16) and 31% (four of 13) improved by at least three lines (odds ratio [OR] = 0.76; P = .752). At postoperative month 6, 43% (six of 14), and 23% (three of 13) improved by at least three lines (OR = 0.38; P = .262). At postoperative year 1, 46% (seven of 15) and 18% (two of 11) improved by at least three lines (OR = 0.25; P = .194).

One patient in the pneumatic ± tPA group had a recurrent submacular hemorrhage after her initial pneumatic ± tPA procedure that was treated with a C3F8 pneumatic displacement followed by intravitreal tPA. She had another submacular hemorrhage that

![Figure 3. Percentage of patients achieving three or more lines of improvement at 1 month, 6 months, and 1 year after either pars plana vitrectomy + tissue plasminogen activator (tPA) group or pneumatic ± tPA.](Image)
was treated with a PPV with subretinal tPA. All of these procedures were performed by Surgeon A. The secondary and tertiary procedures were not included in our analysis. The final vision after the three procedures was light perception. The patient in the pneumatic ± tPA group with the RAM had a vitreous hemorrhage 2 days after receiving intravitreal tPA. This hemorrhage did not clear, so the patient was taken to the operating room for a PPV. During surgery, there was noted to be remaining sub-internal limiting membrane (ILM) blood, so the ILM was incised, and the blood was drained. Postoperative visual acuity was stable at 20/60. One patient in the PPV + tPA group with AMD had a rhegmatogenous retinal detachment 1 month after surgery. This detachment was treated with a PPV and laser, and the patient had a final visual acuity of count fingers.

In the pneumatic ± tPA group, the patient with pathologic myopia did not have an improvement in visual acuity of more than three lines. In the PPV + tPA group, one of the two patients with macroneurysms had an improvement in visual acuity of more than three lines.

**DISCUSSION**

The study was not powered to find a statistically significant difference in improvement of three lines or more between the two groups, but there appeared to be a trend toward better vision with pneumatic displacement and intravitreal tPA. This is especially interesting given the fact that some of the patients in the PPV + tPA group had RAMs, which implies better overall RPE health and would lead one to expect better visual outcomes.

A recent randomized, prospective study by de Jong et al. also compared pneumatic displacement with intravitreal tPA and PPV with subretinal tPA. Both treatment groups in this study received bevacizumab injections at the time of treatment. The study by de Jong, et al had shorter follow up of 12 weeks. Longer follow-up helps obtain a realistic result when evaluating treatment of submacular hemorrhage because many eyes have a large change in vision during the first year. Changing vision could be from regression of the bubble, development of cataract, or progression of AMD. This would be missed in a study with follow-up only for a few months. The starting visual acuity for patients in the study by de Jong et al. was also better than the starting visual acuity of our patients with 17 of 24 of their patients starting with a visual acuity of 20/200 or better. Most importantly, de Jong et al. primarily looked at success of anatomic displacement of hemorrhage, whereas this study was more focused on the percentage of patients with improved visual acuity. Ultimately, however, neither study showed a difference in outcome between treatment methods.

Studies by Fujikawa et al., Mizutani et al., and Fassbender et al. looked at the effects of tPA in patients with submacular hemorrhage, and results were mixed with it not making a difference, increasing the chance of a rebleed, or helping with visual outcome respectively. Our study was unique in that patients in the pneumatic ± tPA group received their pneumatic displacement and intravitreal tPA in a staged process so the effects of each step could be observed. Most patients in the pneumatic ± tPA group in our study returned after intravitreal injection of C3F8 and had not yet had sufficient displacement of their hemorrhage (16 of 18 patients). After injection of tPA, five of the 11 patients who had follow-up photographs had definite clearing of the submacular hemorrhage, and the rest showed partial improvement. The improvement only after injection of tPA implies that tPA does play a role for some patients. Therefore, the argument could be made that they simply needed more time with a face-down position to allow for the C3F8 to take effect.

There has been concern that tPA can lead to retinal toxicity. In our study, we saw nothing to indicate any patients developed retinal toxicity in either treatment group.

Two patients in the pneumatic ± tPA group never required tPA injection. One patient had AMD and had a pre pneumatic visual acuity of 20/200. Visual acuity the day the patient would have received tPA was still 20/200 with a subjective improvement and displacement of the hemorrhage from the central macula. Final visual outcome for this patient was count fingers vision. The second patient had pathologic myopia and had a pre pneumatic visual acuity of 20/200, as well. Again, the hemorrhage was successfully displaced, so tPA was withheld. Ultimate visual acuity improved to 20/125. Although neither of these patients improved by three lines to be considered a “success,” each had anatomic success and did not require tPA with its associated cost and potential risks such as hemorrhage noted above.

A potential factor in the outcome of the patients in the PPV with subretinal tPA group is that postoperative anti-VEGF injections may have had less of an effect than they would in an eye that had not had a vitrectomy. There was no predetermined anti-VEGF injection schedule for our patients making this difficult to compare; in fact, anti-VEGF injections were not even available during the time the first patients in this chart review were being seen. It should be noted that although anti-VEGF injections were not an option for the patients treated early in this study, most
patients received anti-VEGF intravitreal injections after they became available. These were not given at the same time as the procedure, so anti-VEGF injections were not considered a part of the procedure being studied. There was no predetermined anti-VEGF injection schedule due to this being a retrospective study and the fact that the injections were not even available for the first patients in the study. As such, treatment patterns with anti-VEGF injections were very difficult to compare. Surgeon B performed PDT on some patients because these patients were treated prior to the advent of anti-VEGF intravitreal injections. The selection of patients to have intervention with tPA did not change with the additional option of anti-VEGF therapy.

To further comment on the potential effects of anti-VEGF treatments, it could be postulated that patients in the PPV with subretinal tPA tended toward a worse outcome over time because the anti-VEGF injections may have had less of an effect than they would in an eye that had not had a vitrectomy. Another possible contributor to the decline in vision was the development of post-vitrectomy cataract in these patients. Finally, the actual act of injection of fluid into the subretinal space is at least to some extent traumatic and could have long-term consequences in an eye that is at baseline unhealthy, whereas an intravitreal injection does not physically alter the retina in the same way. Of course, there was no actual statistically significant difference between the two groups, so it is possible that the outcome between them is equivalent after all.

One limitation of our study was the relatively small patient population. Another limitation is many of the patients in the study regularly travelled large distances to receive care. Sometimes these patients were managed in the interim by more local comprehensive ophthalmologists, leading to some missing data points throughout follow-up. Finally, there could be inherent bias in the procedure groups, as one surgeon treated all patients in one group, and a different surgeon treated all patients in the second group. The benefit of this design is that each surgeon was performing his preferred approach throughout the study.

Although our results did not show a statistically significant difference between the groups, there was a trend of greater patient improvement at each follow-up time point up to 1 year after treatment with pneumatic displacement and intravitreal tPA injection. Even without statistically significant superiority of the pneumatic ± tPA group, the lack of a difference is clinically relevant. A vitrectomy is a more invasive procedure than a pneumatic displacement, requiring an operating room; it also has all of the risks of associated anesthesia, and development of a cataract if the patient is phakic. A vitrectomy is also more costly. Finally, frequently an operating room may not be immediately available, and a pneumatic displacement can be performed more rapidly in the clinic where the patient is being seen. With the results of this study combined with the results of the recent study by De Jong et al., it is reasonable to choose to perform a pneumatic displacement with or without tPA for a patient with a submacular hemorrhage.

REFERENCES


