• Brief Report •

Pars plana vitrectomy with tissue plasminogen activator for traumatic submacular hemorrhage

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Abstract

● **AIM:** To evaluate visual outcomes of pars plana vitrectomy (PPV) combined with tissue plasminogen activator (tPA)-induced clot lysis and pneumatic displacement for submacular hemorrhage (SMH) in a cohort of closed-globe trauma patients.

● **METHODS:** A retrospective, multicenter interventional case series involving 7 eyes of 7 patients who underwent PPV with subretinal tPA administration for SMH secondary to closed-globe injury were conducted. The primary outcome measure was the change in Snellen visual acuity.

● **RESULTS:** The mean age of patients was 32y (range: 21-51y), with a mean follow-up duration of 4.6mo (range: 1.1-14.9mo). The average best-corrected visual acuity (BCVA) was 20/1020 at baseline and 20/114 at the final visit, respectively (P=0.025). Preoperative BCVA was not a significant predictor of final BCVA (r=0.102, P=0.827). Final BCVA did not differ significantly between patients who underwent PPV within 14d of symptom onset and those who underwent surgery after 14d (P=0.57). All eyes received SF_6 or C_3F_8 gas tamponade.

● **CONCLUSION:** Surgical intervention involving tPA-mediated clot lysis and pneumatic displacement may yield visual benefits in trauma-induced SMH without underlying retinal vascular disease; however, larger prospective studies are warranted to confirm these findings.

● **KEYWORDS:** submacular hemorrhage; subretinal; tissue plasminogen activator; clot lysis; pneumatic displacement

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INTRODUCTION

Submacular hemorrhage (SMH) presents a complex challenge in ophthalmic practice, often resulting in devastating central vision loss. SMH often occurs secondary to underlying choroidal neovascularization (CNV), as seen in conditions like neovascular age-related macular degeneration (nvAMD) and polypoidal choroidal vasculopathy (PCV)[1-3]. However, SMH can occur in scenarios without underlying CNV, such as choroidal rupture and retinal arterial macroaneurysms (RAM)[1-2].

Early animal studies have demonstrated the toxic effects of subretinal hemorrhage on the retina, leading to photoreceptor damage within hours to days of hemorrhage onset[4]. Various methods have been employed to reduce the potential photoreceptor damage and vision loss from subretinal hemorrhage. These include surgical removal of the CNV complex, and pharmacologic agents such as tissue plasminogen activator (tPA). While the submacular surgery trials (SST) demonstrated that there was no benefit in surgical removal of CNV complexes, there has been increasing interest in using tPA as a thrombolytic for SMH from nvAMD with and without vitrectomy[5-13].

Although a number of studies have evaluated the role of pharmacologic clot lysis with tPA and pneumatic displacement with or without vitrectomy in nvAMD, the management of SMH secondary to etiologies other than nvAMD has not been as extensively studied[1-2]. Unlike nvAMD, where SMH is associated with CNV, closed-globe traumatic SMH is not caused by CNV even though CNV can occasionally be a complication of choroidal rupture secondary to the antecedent trauma. Consequently, there is no consensus for the best treatment approach in patients with non-AMD causes of SMH, specifically traumatic SMH. The ideal treatment approach

likely depends on the individual patient characteristics and clinical presentation. As it pertains to traumatic SMH, there are several, small observational studies that suggest potential benefit of various treatment modalities, including pneumatic displacement with and without vitrectomy and intravitreal tPA, pneumatic displacement alone, and observation alone, without consensus regarding the best treatment[14-16]. The aim of this study is to describe the clinical features and outcomes in 7 cases of trauma related SMH that underwent pars plana vitrectomy (PPV) with clot lysis using subretinal tPA and subsequent displacement using a tamponade agent. Our case series also aims to stimulate further investigation of this treatment for non-AMD related SMH. To our knowledge, this is one of the largest case series evaluating this treatment strategy for traumatic SMH.

PARTICIPANTS AND METHODS

Ethical Approval Study approval was obtained from the institutional review board of the participating centers (IRB ID: 202011067) and all research adhered to the tenets of the Declaration of Helsinki. This was a de-identified retrospective study and the Institutional Review Boards did not require individual patient consent for collection of de-identified retrospective data.

Participants A retrospective observational study was performed on patients with closed-globe injury SMH who underwent PPV with clot lysis using subretinal tPA and subsequent displacement using a tamponade agent. All patients had their surgical intervention between May 2016 and April 2021.

Once patients were properly identified, electronic health records were reviewed including age, gender, diagnosis, and time from symptom onset to intervention. All patients underwent ophthalmic exams before and after surgery and best corrected visual acuity (BCVA) was recorded at all possible time points, including pre-surgery, 1, 3, 6mo, and the final clinic visit. Count finger vision and hand motion were extrapolated to a minimum angle of resolution (logMAR) of 2.0 and 3.0 respectively, and any statistical analysis was performed using logMAR and converted back to Snellen acuity for clinical relevance. The primary outcome measure was the final BCVA at most recent follow-up visit. Thickness (μm) and size at the greatest width (μm) of the hemorrhage were measured by optical coherence tomography (OCT). The cohort was further divided into 2 groups for analysis according to the age: greater or less than 30 years old, time from symptom onset to the date of surgical intervention: those patients who underwent clot lysis and displacement at 14d or less and those patients after 14d, and time of follow-up from surgical intervention: greater or less than 3mo.

Surgical Technique The exact surgical technique employed varied by provider. In general, the technique employs a standard three-port, 25-gauge PPV system. After core vitreous and posterior hyaloid removal, a subretinal injection cannula with a 41-gauge tip was used to create a retinotomy and inject tPA (concentration 12.5 mg/0.1 mL) into the subretinal space until an adequate bleb was visible, typically around 0.3 mL of tPA. The tPA syringe was connected to the vitrectomy system under the viscous fluid control option with low flow settings to allow precise control of the subretinal injection by the primary surgeon; however, an assistant operated manual injection technique was also used with the primary surgeon holding the subretinal cannula. A tamponade agent such as air, gas, or silicone oil, was injected at the conclusion of the case. Postoperative positioning involved an initial supine period for 45 to 60min following subretinal tPA injection, followed by upright positioning with the patient instructed to look straight ahead for 3 to 4h. Subsequently, patients were advised to maintain a face-down or lateral position overnight, with positioning tailored to the size and location of the hemorrhage.

Statistical Analysis Data were analyzed using SPSS software (version 29; IBM Corporation, Armonk, NY, USA) and R Studio (version R-4.2.1). Given the small sample size, nonparametric analyses were predominantly performed. Results for age, initial visual acuity, final visual acuity, thickness of SMH at fovea (μm), width of SMH (μm), and time from symptom onset to intervention (days) did not violate the assumption for a normal distribution (Shapiro-Wilk test, $P>0.05$). Pre-operative, 1-month post-operative, and final follow-up visit BCVA were compared using the Wilcoxon signed-rank test. Visual outcomes for patients ≤14d and >14d from traumatic event to intervention was compared using one-tailed Mann-Whitney *U* test. A simple linear regression model was used to correlate final BCVA with initial BCVA, SMH thickness, SMH width, and time from symptom onset to intervention, and multi-variate linear regression models were performed as appropriate. Pearson correlation coefficient and nonparametric analyses Wilcoxon signed rank test and Mann-Whitney *U* were performed where appropriate and *P* value less than 0.05 was considered statistically significant.

RESULTS

Seven patients were included in this study, all of whom underwent PPV and subretinal tPA injection after closed-globe injury SMH due to primary choroidal rupture. The majority of hemorrhages were predominantly subretinal, with the remainder exhibiting a mixed picture of clinically significant subretinal hemorrhage with a component of sub-retinal pigment epithelium (RPE) hemorrhage. The demographics, characteristics, and outcomes for the patients are listed in Table 1.

The mean age was 32 years old (range 21-51y). Mean time from symptom onset to intervention was 26.1±16.4d (range 10-56d). Three patients (43%) underwent surgery within 14d

Table 1 Patient demographics and characteristics

Patient number	Age (y)	Sex	Laterality	Diagnosis	Intervention (in addition to PPV, SR tPA, and tamponade)	Tamponade agent	Days from symptoms to Intervention	Baseline visual acuity	Final visit visual acuity
1	21	M	OD	Traumatic	-	12% C_3F_8	56	HM	20/200
2[a]	33	M	OS	Traumatic	-	12% C_3F_8	33	20/60	20/200
3	25	F	OS	Traumatic	-	12% C_3F_8	33	CF	20/20
4	32	F	OD	Traumatic	-	12% C_3F_8	14	CF	20/160
5	27	M	OS	Traumatic	Glued secondary IOL	20% SF_6	26	20/400	20/200
6[b]	51	F	OD	Traumatic	ILMP, Avastin	14% C_3F_8	10	CF	20/400
7	38	M	OS	Traumatic	EL, Avastin	18% SF_6	11	20/300	20/25

[a]Patient developed a full thickness macular hole that was repaired, however was lost to follow-up following macular hole repair; [b]Patient developed a full thickness macular hole and final visual acuity was recorded after the patient underwent macular hole repair. CF: Counting fingers; EL: Endolaser; HM: Hand motion; ILMP: Inner limiting membrane peeling; IOL: Intraocular lens; OD: Right eye; OS: Left eye; PPV: Pars plana vitrectomy; SR: Subretinal; tPA: Tissue plasminogen activator.

of symptom onset. Average length of follow up after surgery was 4.6mo (range 1.7-14.9mo). Three patients (46%) were lost to follow-up within 3mo of surgery, but all patients had at least 1mo of follow up.

Patients underwent gas tamponade following PPV with subretinal tPA with either non-expansile octafluoropropane (C_3F_8) or sulfur hexafluoride (SF_6). Two patients (15%) with traumatic SMH received intravitreal bevacizumab at surgery as per surgeon preference based on concern for potential development of CNV. Two patients (patient 2 and 6) required a second intervention of PPV and ILM peeling with C_3F_8 gas tamponade due to full thickness macular holes. There were no other significant complications related to the intervention. Figure 1 shows an example of a patient with closed globe injury and a sub-retinal hemorrhage with suspected choroidal rupture based on biomicroscopy and imaging.

Following surgery at 1-week post-operative visit, excellent displacement of the hemorrhage with a clearly visible choroidal rupture on the clinical photograph can be seen with resolution of the sub-retinal hemorrhage (Figure 2).

Given clinical history and structural optical coherence tomography (OCT) findings of these cases, the vision loss seemed to be due primarily to SMH and not due to other secondary findings such as vitreous hemorrhage, and such resolution would lead to BCVA improvement. As such, there was a significant overall improvement in mean BCVA from 20/1020 at initial presentation to 20/114 at final follow up (P=0.025). Similarly, there was a significant improvement at the 1mo postoperative follow up from 20/1020 at initial presentation to 20/135 (P=0.039). Six patients (86%) had improvement in BCVA greater than two Snellen lines. The remaining patient had worsening BCVA from 20/60 to 20/200 due to a full thickness macular hole that was repaired, and follow-up BCVA was not obtained because the patient was lost to follow-up. Correlation between preoperative BCVA as a predictor of final postoperative BCVA outcome was not statistically significant (r=0.102, P=0.827). Only one eye had baseline vision better than 20/200 at the initial visit, whereas 6 eyes achieved 20/200 or better vision at the final visit.

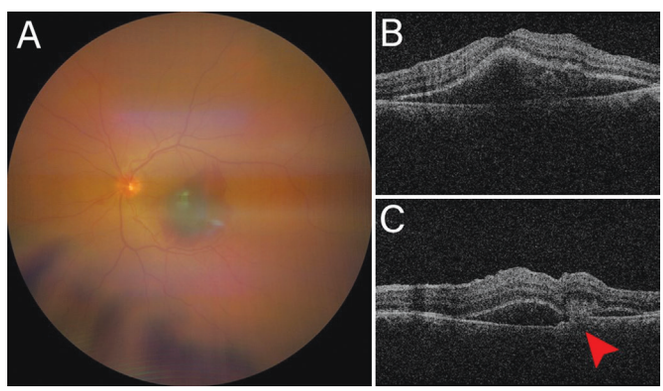

Figure 1 Submacular hemorrhage after closed globe-trauma Fundus photograph demonstrates a fovea-involving sub-retinal hemorrhage and a faintly visible choroidal rupture in a patient with closed globe injury (A). OCT images demonstrate a large sub-retinal hemorrhage (B) and the site of the choroidal rupture (C, arrowhead). OCT: Optical coherence tomography.

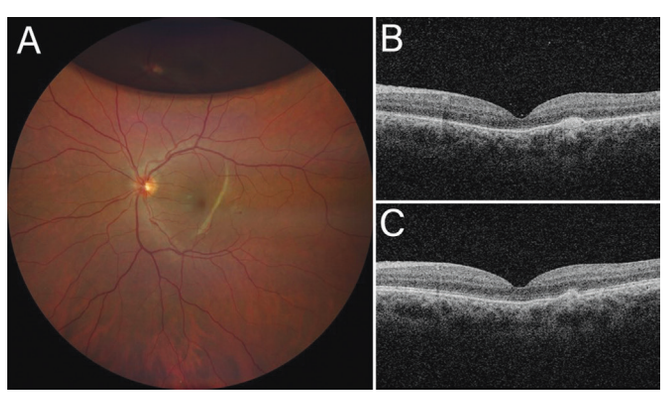

Figure 2 Choroidal rupture after closed-globe trauma Fundus photograph one week after surgery demonstrates complete displacement of sub-retinal hemorrhage and an extrafoveal choroidal rupture (A). OCT images demonstrate resolution of the sub-retinal hemorrhage and the site of the choroidal rupture at one week (B) and one month (C). OCT: Optical coherence tomography.

When stratifying by age, patients under the age of 30y had a mean improvement in BVCA from 20/2517 to 20/133 and those 30y or older had a mean improvement from 20/514 to 20/93; however, there was no statistically significant difference between the two groups (P=0.85). Additionally, there was no difference between those who had a follow-up >3mo compared to those <3mo (P=0.85), both potentially due to the small cohort sample size. Final BCVA for those whose surgical intervention was within 14d of traumatic event was not significantly different from those after 14d (P=0.57). Moreover, BCVA in patients with a time to surgical intervention of less than 1mo was not statistically different compared to after 1mo (P=0.96).

Additional univariate linear regression analysis was performed, and there was no significant association between visual acuity outcomes and SMH thickness (P=0.55), presenting visual acuity (P=0.827), width of SMH (P=0.40), and time from symptom onset to intervention (P=0.89). A multivariate linear regression analysis was performed utilizing the same variables; however, the model was not statistically significant (P=0.92). Additionally, there was also no significant association when looking at these correlations in terms of Snellen line improvement (P>0.05).

DISCUSSION

Our study suggests that surgical intervention with surgical clot lysis and pneumatic displacement may be beneficial in patients with traumatic SMH. Although there was a statistically significant overall improvement in BCVA, the average final BCVA was 20/114, indicating moderate visual morbidity in these patients even after intervention. Two patients (28%) had final BCVA of 20/25 or better; however, the remainder of patients had final BCVA of 20/160 or worse. These results are comparable with case series evaluating other treatments for trauma induced SMH, namely intravitreal tPA and pneumatic displacement or pneumatic displacement alone, which have yielded near complete visual restoration in select patients and continued visual morbidity in others[14-15,17]. There is limited, low-level evidence available regarding outcomes of observation alone for traumatic SMH and suggests vision may improve without intervention, with one case series of two eyes showing a mean visual acuity improvement from 20/252 to 20/40 at week six of observation[16]. Comparative studies with larger cohorts are needed to determine treatment superiority. Furthermore, in our cohort, presenting BCVA was not predictive of final visual outcome (P=0.83). This is in contrast to existing literature evaluating all-cause SMH which suggests an association between pre-treatment BCVA and final BCVA[18-19]. Currently, there is a lack of consensus in the literature regarding other potential prognosticators of final BCVA including patient age and SMH size[19]. In our patients with traumatic SMH, however, age and SMH width and thickness were not associated with functional outcomes.

Animal models have demonstrated that damage from SMH is caused by iron toxicity on photoreceptors, reduced nutritional exchange between choriocapillaris and the retina, and clot contraction leading to shearing of photoreceptors[1,4,10,20-21]. There is evidence that SMH displacement within 14d of hemorrhage onset may have more favorable outcomes and natural studies in nvAMD have shown poor outcomes when SMH is left untreated, particularly in the setting of larger and thicker hemorrhages[4,22-24]. Currently, there is mixed literature on the outcomes of SMH due to other causes such as trauma, and our cohort did not demonstrate improved outcomes with earlier intervention (<14d to surgery) or smaller SMH size in a traumatic SMH cohort as suggested by previous studies[25-26].

Early surgical interventions for macular hemorrhage also had mixed outcomes[7,9,11]. The submacular surgery trial (SST): Group B was a randomized control trial published in 2004 aiming to better define the role of surgery versus observation for SMH in nvAMD, but was carried out prior to the widespread use of anti-vascular endothelial growth factor (VEGF) in nvAMD[5,23]. The trial found no benefit from the surgical extraction of hemorrhage and CNV lesions compared to observation, however the use of tPA and tamponade agent was not standardized. Patients in the SST had relatively high rates of complications, including rhegmatogenous retinal detachment in 16% of the patients. Since the SST, surgical interventions have tended towards smaller gauge vitrectomy and so earlier historic studies may not be as clinically relevant in terms of all surgical outcomes. In our cohort, patients 2 and 6 (28%) required repeat PPV due to full thickness macular hole, however no other surgical complications occurred in our cohort.

Although CNV related SMH represented up to 90% of cases, the pathogenesis of CNV-related and non-CNV-related SMH differ[1-3]. In cases of CNV, anti-VEGF as monotherapy or with pneumatic displacement may be beneficial to control the underlying pathology[13,27-28]. It would be reasonable to presume that anti-VEGF would not be beneficial in patients without CNV such as in this traumatic SMH cohort and different treatment strategies are required. Although anti-VEGF has been evaluated in traumatic SMH cases without CNV with varying functional outcomes, strength of available evidence for this treatment is low[29]. In our cohort, two patients with history of trauma underwent anti-VEGF therapy at the time of surgery; however, this was based on surgeon preference as a prophylactic measure and these patients did not require subsequent anti-VEGF therapy.

There are multiple limitations to our study, including the retrospective nature and limited number of study patients given

the rarity of this pathology. Additionally, angiography was performed but not standardized among all patients. The patient history, noninvasive imaging, and clinical exam were used to confirm the absence of CNV and/or the non-AMD diagnosis. Notably, there was no control group, and it is uncertain if some patients would have had favorable or similar outcomes even without surgical intervention. However, given the relative safety of smaller gauge vitrectomy and data that may suggest beneficial outcomes with earlier clot displacement in nvAMD, the surgeons at our institutions tend to favor interventional treatments rather than observation in patients that present with thick SMH, especially within the first few weeks of symptom onset. Finally, though surgeries were performed in a similar manner, surgical technique was not completely standardized and was performed based on surgeon preference.

Overall, this study adds to the current literature regarding non-AMD causes of SMH and demonstrates that surgical intervention may improve visual outcomes in traumatic SMH; however, it is important to note that many of these patients often suffer permanent visual morbidity despite intervention due to other complications such as traumatic optic neuropathy. Further studies are required to better understand the role of surgical therapies in those with SMH, particularly in patients with traumatic SMH and other non-AMD etiologies. Given the rarity of these patients, a larger multi-center series or prospective trial may be beneficial to better elucidate the effect of interventional therapies in this patient population.

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