# Management of Sub Macular Hemorrhage with Intravitreal Injection of Tissue Plasminogen Activator and Sulfur Hexafluoride

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## ABSTRACT

**Purpose:** To evaluate the clinical outcome in terms of anatomical displacement of sub macular hemorrhage(SMH) and visual outcomes of intravitreal tissue plasminogen activator (tPA) and expansile gas Sulfur hexafluoride(SF6) injection as a minimally invasive treatment for SMH of duration one week or less .

**Design:** Retrospective non-comparative interventional case series.

**Materials and Methods:** This study was a retrospective clinical case series examining 44 eyes that received an intravitreal injection of 100 mcg of tPA and $SF_6$ for SMH. The main outcomes evaluated were visual acuities (VA), anatomic displacement of sub macular blood, and complications. Results: Age related macular degeneration was the etiological diagnosis in 38.5% eyes followed by trauma in 27%.Comparison of SMH size on pretreatment versus on first week follow up revealed reduction of size in majority from 2 disc diameters pretreatment in 38.6% eyes to 1 disc diameter post-treatment in 59.1% eyes. However the shifting of the SMH was observed in all cases. This was seen translating into visual gain with 31.8% eyes gaining 1-2 Snellen lines, 18.2 % gaining 2-3 lines and 13.5 % gaining 3-5 lines. Major complication was noted in 2 cases (Rebleed and break-through vitreous hemorrhage in one each).

**Conclusion:** Intravitreous injection of tPA and gas, followed by a brief period of prone positioning, is effective in displacing thick blood from beneath the centre of the macula. The procedure is technically simple, and the rate of serious complications appears to be low. Most patients enjoy visual improvement coincident with blood displacement.


**Key words:** Sub macular hemorrhage, tissue plasminogen activator, $SF_6$ gas.

## INTRODUCTION

Sub macular haemorrhage (SMH) complicates a range of ocular conditions, most commonly age related macular degeneration (AMD), retinal artery macro aneurysm, trauma, presumed ocular histoplasmosis syndrome, and high myopia.[1] Damaging effects of sub retinal blood has been attributed to a multitude of causative factors including chemical toxicity of iron, traction on photoreceptors from the enmeshed fibrin, physical barrier to diffusion of nutrients and metabolites and photoreceptor lipids being attacked by iron-catalyzed free radicals through the Fenton reaction.[2-7]

The pioneering work on intravitreal use of tissue plasminogen activator (tPA) for SMH was done by Heriot who in 1996 presented the results from a small clinical series of this novel outpatient procedure of intravitreal tPA and perfluoropropane gas injection for the treatment of SMH. Heriot proposed that the intravitreal tPA would enzymatically liquefy the sub macular blood, which would then be pneumatically displaced inferiorly in the sub retinal space without vitrectomy. His initial experience suggested a high anatomic success rate (blood displacement in 19 of 20 eyes) with few complications.[8]


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## MATERIAL AND METHODS

We reviewed the medical records of 44 eyes from 44 consecutive patients from our records at a tertiary care vitreoretina centre, who had undergone intravitreal injection of commercial tPA solution and SF6 gas for thrombolysis and displacement of SRH of duration one week or less between 2001 and september 2013.

The preoperative ophthalmic examination involved determination of the best-corrected visual acuity (VA) using a linear Snellen chart, biomicroscopy, and indirect ophthalmoscopy. All the clinical findings were documented in patients clinical record sheets with proper color coded retinal drawings of either eyes Color fundus photography were performed for all cases pretreatment, on the first day post injection and on consequent visits.

The procedure was carried out in operation room by retinal consultants. Peribulbar block was given. Betadine irrigation of the conjunctival cul de sac, the eyelids, and the eyelashes was performed. The injection is available as 20 mg powder along with 20 ml of sterile distilled water. The lyophilized material was reconstituted with sterile water to get a concentration of 1 mg/mL. 0.1 ml (100 micrograms) of this injection was taken in a 1 cc syringe and was injected into mid vitreous cavity with the 26 gauge needle. Site of injection was 3.5 mm away from limbus in aphakic and pseudophakic eyes and 4 mm in case of phakic eyes. After injecting tpa, the same entry and needle was used to inject SF6 gas (0.4 ml of 100% gas). An anterior chamber paracentesis was then performed . After ensuring optic nerve head perfusion, betadine drop was applied, the eye was covered with a sterile eye pad, and the patient was allowed home.

Postoperatively, patients were instructed supine position for 2-3 hrs. In the late evening, the patients were instructed to begin prone posturing as much as possible. All patients were reviewed the following day. If the submacular blood had not completely displaced 24 hours postoperatively, the patients were advised to continue prone posturing for a further 24 to 48 hours. These patients were then examined at 1 week, 1 months after the procedure. On every visit indirect ophthalmoscopy and fundus photography was performed. The main outcomes evaluated were the extent of blood displacement from under the fovea, VA preoperatively, 1 month.

On follow up visits the fundus examination and ancillary investigations to ascertain etiology of SMH was done depending on the media clarity as well as the amount of displacement of SMH. This included mainly fundus fluorescein angiography and optical coherence (OCT) tomography (for those cases who were seen in the period after OCT was available).

Once the cause was known the patient was accordingly treated. Exudative AMD was clinically diagnosed on presence of choroidal neovascular membranes, drusens and Retinal Pigment Epithelial changes. Patients who were diagnosed as AMD, were evaluated on FFA as to whether the leaking choroidal neovascular membranes were extrafoveal ,juxtafoveal or subfoveal. In pre anti VEGF era, the extrafoveal and juxtafoveal membranes were treated with lasers and the subfoveal membranes required trans pupillary thermotherapy. However over recent years all exudative AMD cases were investigated mainly on FFA, ICGA and OCT and were managed with intravitreal anti-VEGF injections. Retinal artery macroaneurysms were lasered.

## RESULTS

A total of 44 eyes of 44 subjects with SMH of a duration of one week or less were included in the study. Males were 35 (79.5%) and Females were 09 (20.5%).Most of the patients (61.4%) were in the age group 40-79 years. Follow up duration ranged from as low as 30 days to 300 days with most of the cases (61.4%) being followed up to 100 days.

### 1. Underlying etiology of SMH

Age related macular degeneration was the cause of SMH in majority 17 (38.5%) of the eyes (Figure 1, 2). Others were trauma in 12 (27%) eyes (Figure 3,4), Retinal artery macroaneurysm in 6 (13.9%), Ideopathic polypoidal vasculopathy in 5 (11.3%) , following scleral buckling in 3 (7%) and Myopic choroidal neovascular membrane in 1(2.3%), ( Figure 5).

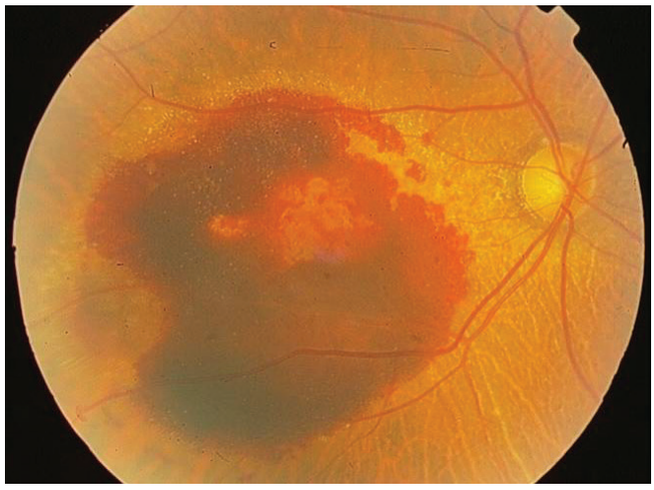

***Figure 1:*** *Pre-treatment subretinal haemorrhage size as on fundus picture.*

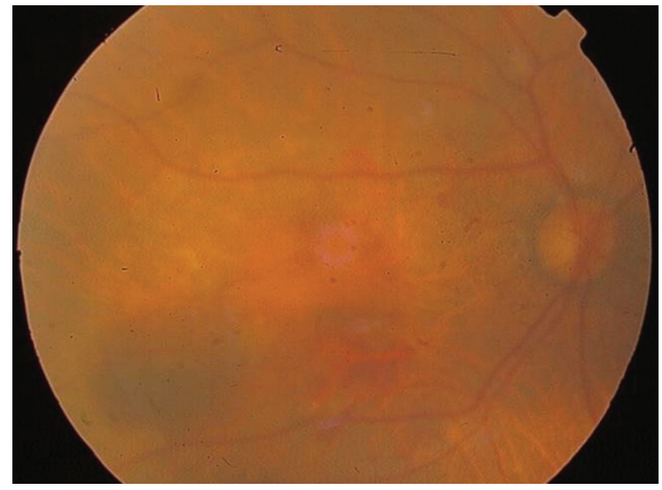

***Figure 2:*** *Color fundus photograph of the right eye of a case of Age Related Macular Degeneration with Submacular hemorrhage following treatment with intravitreal injection of tissue plasminogen activator with sulfur hexafluoride gas showing inferiorly displaced blood.*

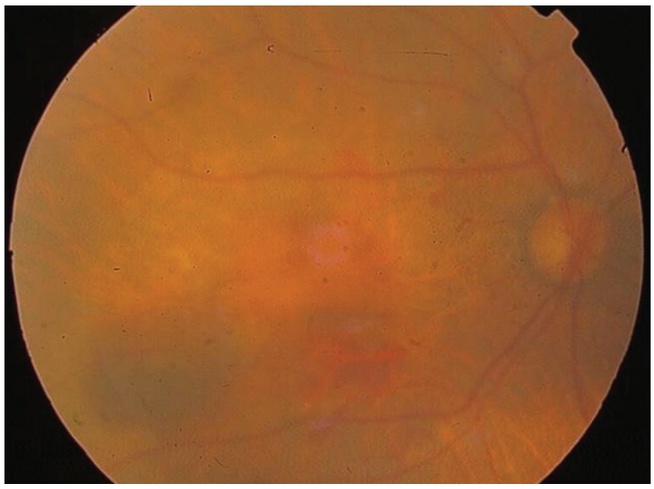

*Figure 3: Color Fundus photograph of the Left eye with Post traumatic Submacular hemorrhage.*

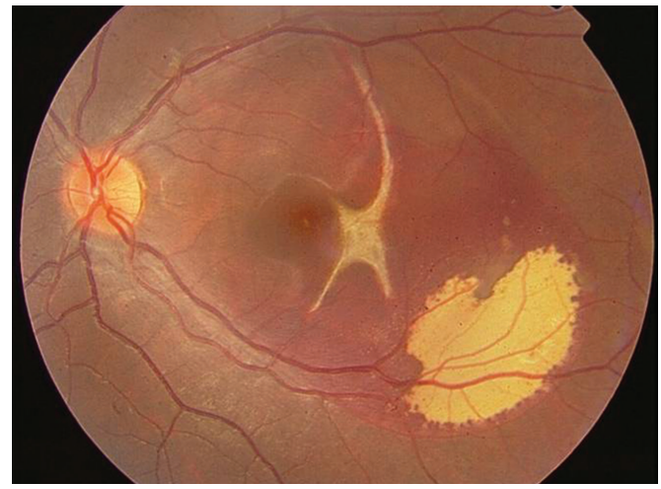

*Figure 4: Color Fundus photograph of the Left eye with Post traumatic Submacular hemorrhage after intravitreal injection of tissue plasminogen activator with sulfur hexafluoride gas revealing choroidal rupture.*

| ETIOLOGY | NO.OF EYES |
|---|---|
| AMD | 17(38.5%) |
| TRAUMA | 12(27%) |
| RUPTURED RAM | 6(13.9%) |
| FOLLOWING BUCKLING | 3(7%) |
| IPCV | 5(11.3%) |
| BLED MYOPIC CNVM | 1(2.3%) |

*Figure 5*

### 2. Effect of the treatment on the size of SMH

On presentation, the size of SMH as measured in comparison to size of optic disc designated as "DDs" was noted to be 1 DD in 5 (11.4%), 2DD in 17 (38.6%), 3 DD in 9(20.5%), 4DD in 7 (15.9%) ,5 DD in 3 (6.8%) and 6 DD in 3 (6.8%) eyes.

Following one week of the treatment, the size of SMH was noted to reduce being nil in 10 (22.7%),1 DD in 26(59.1%) and 2DD in 8 (18.2%) eyes. No eye was found to have SMH more than 2 DD size.

Thus there was a clear reduction in size of SMH with treatment as is depicted in the graph (Figure 6).

### 3. Effect of the treatment on visual acuity

Pretreatment logMAR visual acuity was less than 1 in 22(50%) ,1.30 to less than 1 and 1 to less than 0.48 in 11(25%) each and more than or equal to 0.48 in none of the eyes.

One week following the treatment 6 (13.6%) eyes had a logMAR vision less than 1.30, 03 (6.8%) eyes had vision 1.30 to less than 1, 20 (45.5%) eyes had a vision 1 to less than 0.48&15 (34.1%) eyes were noted to have a visual acuity of more than or equal to 0.48 .

Thus proportion of eyes on lower side of the visual acuity reduced following treatment.

It was further appreciated in terms of gain of Snellen lines of visual acuity with 6(13.5%) eyes gaining 5-6 lines, 08(18.2%) eyes gaining 3-4 lines, 14(31.8%) eyes gaining 1-2 lines&16 (36.5%) eyes showing no improvement in visual acuity (Figure 7).

### 4. Associated Complications

Vitreous cavity hemorrhage/breakthrough hemorrhage was seen in 1 (2.3%), Rebleed in 1 (2.3%) and RPE Changes/ mottling in 2 (4.6%) eyes.

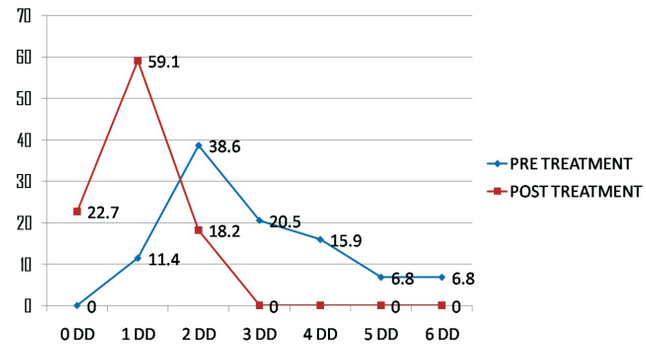


*Figure 6*

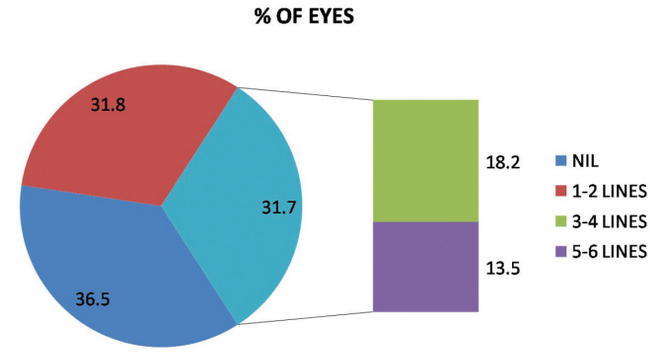


*Figure 7*

## DISCUSSION

In 1999, we reported first case of SRH successfully treated and benefitted from this therapy in a case of SMH secondary to Age related macular degeneration.[9]

Those days since spectral domain optical coherence tomography was not available for evaluation of these cases preoperatively, clinical differentiation was relied upon to grade the density of hemorrhage. However in present day practice an optical coherence tomography is a must in preoperative evaluation of these cases primarily to differentiate between a sub retinal and a sub retinal pigment epithelial bleed. This differentiation is critical since the outcome and prognosis is guarded in the later. OCT is also critical in evaluation of the etiological disorder especially AMD, in order to ascertain activity of the disease.

Present case series showed distinct anatomically success in terms of shifting of SMH on first post injection day that was seen in all but one case which had a breakthrough vitreous hemorrhage. Marked reduction in size of SMH as documented on first week follow up with 81.8% eyes having a SMH between nil to 1 DD in size.

Visual gain of varying degree was appreciated by 63.5% of the eyes. Non improvement in vision of remaining 36.5% eyes was due to AMD and vision threatening features thereof as etiological feature. AMD was diagnosed clinically by presence of drusens, neovascular membranes. Clinical findings were confirmed on FFA as classic or occult leaks located either juxtafoveally/subfoveally or extrafoveally.AMD was associated with poor visual outcome. One patient of AMD rebled twice after the treatment necessitating a vitrectomy and choroidal neovascular membrane removal. The final anatomical results were successful in this case. This case was a hypertensive and had ischaemic heart disease and was using aspirin, suggesting the role of systemic issues in severity of the disease. This case was treated in pre-anti VEGF era when we did not have much of options to choose from but for lasers for juxta/extrafoveal membranes) or transpupillary thermotherapy for sub-foveal membranes. However no such case was seen in after anti anti VEGFs were in regular use (2005 onwards).

We saw no evidence of retinal or other intraocular toxic reactions to tPA solution in the doses 100 μg in 0.1 ml . Nevertheless, the potential for retinal toxicity from the commercially available tPA solution remains a serious concern. Johnson and coworkers reported dose-dependent retinal toxicity in rabbit eyes with intravitreous injections of 50 μg/0.1 ml or greater, including severe retinal necrosis at higher concentrations. The toxic reaction was attributed to the arginine-based vehicle of the commercial tPA solution.[10]

Recent observation shows that intravitreous gas without tPA effectively displaces submacular hemorrhage in some cases, raises a question about the role for intravitreous tPA in this procedure.[11]

Several lines of evidence suggest that intravitreous tPA is capable of traversing the retina in at least some species. The molecular weight of tPA (70 kD) is similar to that of albumin (68 kD), a protein that has been shown to diffuse across intact rabbit retina from the vitreous cavity.[12] Only a prospective, randomized, clinical trial will establish which, if any, eyes require intravitreous tPA adjunctive therapy to facilitate complete pneumatic displacement of submacular blood. However, we believe it is unlikely that intravitreous gas without tPA will produce complete displacement in all eyes, particularly those with freshly clotted blood.

## CONCLUSION

We speculate that intravitreal injection of tPA and $SF_6$ for the management of SMH physically shifts the subretinal blood away from the fovea and minimizes disciform scar formation and the possible toxicity associated with subfoveal blood. This also help to ascertain the etiological association of SMH, which has important therapeutic implications. In this series, intravitreal tPA and expansile gas injection was successful in achieving anatomic displacement of submacular blood.

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