

# Can intravitreal tissue plasminogen activator and SF6 gas facilitate management of macular degeneration with photodynamic therapy?

M.M.K. MUQIT, F.D. GHANCHI

Medical Retina Service, Department of Ophthalmology, Bradford Teaching Hospitals, NHS Foundation Trust, Bradford, Yorkshire - UK

**PURPOSE.** *To describe the safety and efficacy of intravitreal tissue plasminogen activator (tPA) and sulfur hexafluoride (SF6) gas with sequential photodynamic therapy (PDT) in the management of submacular hemorrhage (SMH) associated with macular degeneration (MD).*

**METHODS.** *Consecutive case series of five patients presenting with acute SMH from neovascular MD between May 2004 and January 2006 in a UK Eye Centre. Duration of visual loss was less than 7 weeks. Treatment involved intravitreal injections of tPA, SF6 gas to achieve pneumatic displacement of SMH, and 24 hours prone posturing. Displacement of SMH was assessed by digital photography, and choroidal neovascularization (CNV) was reclassified using angiography. PDT was applied when indicated within 1 to 12 days postoperatively.*

**RESULTS.** *Adequate displacement of SMH allowed visualization of CNV within 24 hours in three of five patients. One patient with large SMH of 7 weeks duration had partial displacement of SMH. Three patients were reclassified with classic CNV after tPA-SF6 injection, and successfully underwent PDT.*

**CONCLUSIONS.** *Intravitreal tPA and SF6 assisted pneumatic displacement of SMH is a safe and effective intervention. This technique facilitates more accurate angiographic classification of CNV. PDT may be sequentially and rapidly applied as early as 1 day after injections. The technique may be offered to patients with neovascular MD presenting with acute SMH. (Eur J Ophthalmol 2008; 18: 591-4)*

**KEY WORDS.** *Photodynamic, Submacular hemorrhage, Sulfur hexafluoride, Tissue plasminogen*

*Accepted: January 4, 2008*

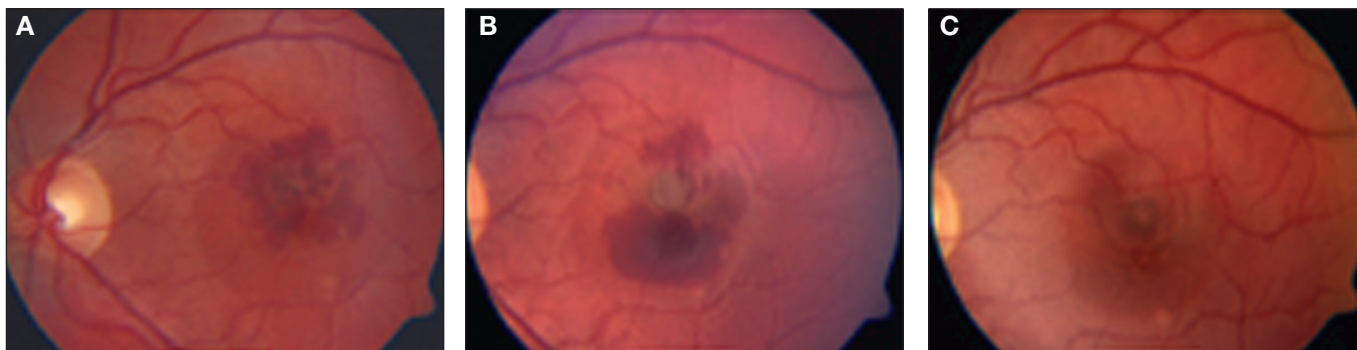
## INTRODUCTION

The current treatment of acute submacular hemorrhage (SMH) arising from macular degeneration (MD) can be challenging in the United Kingdom (UK). Submacular surgery (1) and tissue plasminogen activator (tPA) with expansile gas (2-7) have been attempted to improve vision, but results have been disappointing. A key issue in patients with SMH in MD surrounds the delay in accurate diagnosis of neovascular complex. The natural history of SMH is poor due to slow spontaneous resolution of blood and toxic effects on photoreceptors. We report the results of intravitreal tPA and sulfur hexafluoride (SF<sub>6</sub>) gas in pa-

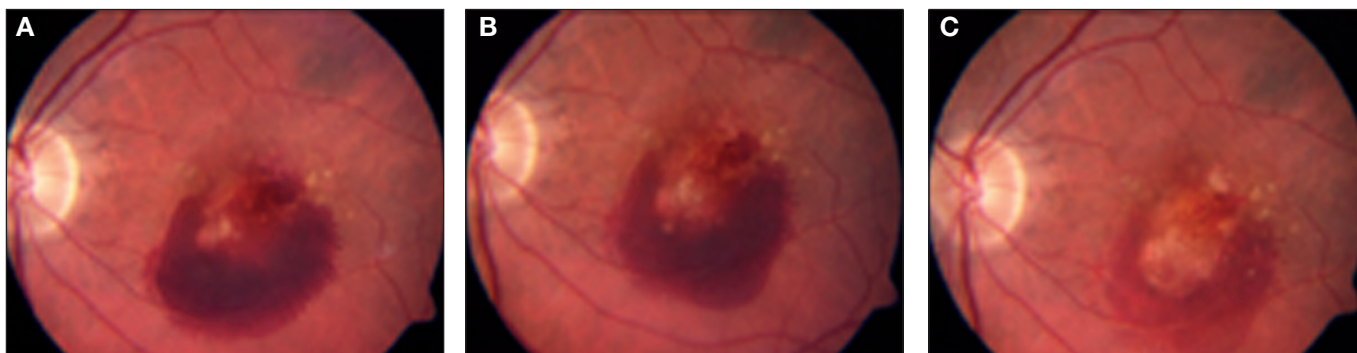
tients presenting with acute SMH. We explore the efficacy of clearing the blood and the sequential application of photodynamic therapy (PDT).

## METHODS

Five consecutive patients presenting with SMH from neovascular MD were treated. Povidone iodine was used with subconjunctival 2% lignocaine. A paracentesis was performed, and intravitreal injection of 25 µg/0.1 mL tPA (Actilise®, Boehringer-Ingelheim) and 0.3 mL 100% SF<sub>6</sub> gas (Arceole®, Arcad Ophta, France) were used for all pa-



**Fig. 1 - (A)** Pretreatment appearance of submacular hemorrhage in the left eye of a 34-year-old woman with idiopathic macular degeneration. **(B)** There was complete displacement of hemorrhage 24 hours after treatment with intravitreal tissue plasminogen activator and SF6 gas followed by face down posturing. **(C)** At 6 months the condition remained stable with no recurrence of hemorrhage.



**Fig. 2 - (A)** Pretreatment mixed density submacular hemorrhage with thick and thin blood components. **(B)** At 1 week there is partial clearance centrally around the fovea. **(C)** At 3 months there is disciform scar formation at the macula with persistent hemorrhage.

tients. Slow pars plana injections were delivered into the mid-vitreous cavity, 3.5 mm from the limbus in the inferotemporal quadrant. Optic nerve head perfusion was checked using indirect ophthalmoscopy. Patients were instructed to follow a regimen of 24 hours prone posturing. Blood displacement was defined as the amount of clearance of hemorrhage from the macula to allow adequate angiographic visualization of the central macula.

## RESULTS

Patient clinical characteristics are shown in Table I. Five patients (age range 33 to 85) presented with acute SMH due to age-related MD (AMD) (Cases 1–4) and idiopathic MD (Case 5). Mean pretreatment duration of symptoms was 13.8 days. Mean preoperative ETDRS vision was 30 letters, and mean postoperative vision at both 1 week and 1 year was 45 letters. Complete displacement allowed vi-

sualization of choroidal neovascularization (CNV) within 24 hours in three of five patients. Postinjection fluorescein angiography in these three patients showed classic CNV, and they underwent uncomplicated PDT. Two patients received PDT after 24 hours, while the third patient received PDT 1 week later. One patient (Fig. 1) gained 46 letters of vision at 1 year. Two patients had partial displacement of SMH with visualization of occult CNV (Fig. 2) and PDT was not deemed suitable.

## DISCUSSION

Acute SMH is a difficult condition for clinicians to treat. In current practice within the UK, conservative management may be distressing for patients because of the unknown period of observation before available ophthalmic treatments may be considered. Early diagnosis and treatment of underlying CNV is key to improving final visual out-

**TABLE I - PATIENT CLINICAL CHARACTERISTICS AT PRESENTATION AND AFTER tPA-SF6 INJECTION**

Patient	Age (y)/sex	Duration (days)	Displacement	Fellow macular status	ETDRS vision preop (letters)	ETDRS vision 1 week postop (letters)	ETDRS vision (letters) at 1 yr follow-up	Timing of PDT (days)	CNVM diagnosis postop
1	80/M	5	Adequate	Disciform scar	35	50	52	12	Classic
2	93/F	42	Partial	Disciform scar	7	15	11	Nil	Occult
3	76/F	14	Adequate	Dry AMD	20	30	31	7	Classic
4	83/M	1	Partial	Disciform scar	52	69	50	Nil	Occult
5	34/F	7	Adequate	Drusen	34	63	80	1	Classic

ETDRS = Early Treatment Diabetic Retinopathy Study; PDT = Photodynamic therapy; CNVM = Choroidal neovascular membrane; AMD = Age-related macular degeneration

comes. Prior to PDT availability, the aim of treatment was to clear the macula to improve vision. There is a narrow window of opportunity to treat patients with acute SMH. Blood is toxic to the retina and prevents retinochoroidal nutrient transfer, and SMH duration is a predictor of visual recovery (8). The blood coagulum exerts tractional forces on the photoreceptor outer segments, and iron from hemoglobin has toxic effects on photoreceptors. Visual function may still be poor due to CNV progression and subretinal rebleeding.

Intravascular tPA has been used to treat myocardial infarction and ischemic stroke, where its thrombolytic action allows tissue reperfusion. This action is utilized to remove SMH with vitrectomy (2-4) or to displace it (5, 6). Vitrectomy with subretinal tPA injection has been associated with high rates of recurrent hemorrhage, and has limited efficacy in large SMH, especially subretinal pigment epithelial hemorrhage (2).

The use of intravitreal tPA with short lasting expansile gas (SF<sub>6</sub>) is a less invasive alternative (7, 9), and would allow early angiographic identification of the neovascular complex and PDT application as indicated. Patients are required to maintain face-down posture for 24 hours to achieve macular tamponade by the gas bubble. Early PDT may reduce risk of further bleeding by inducing CNV closure. In our series, PDT was safely undertaken 24 hours postoperatively. None of our patients had secondary bleeding or any related side effects. The efficacy of PDT was not adversely affected in the three treated patients. In all cases, SMH displacement was associated with minimization of the central scotoma and improved vision at 1 week postoperatively.

Our results demonstrate that despite adequate clearance

of SMH, visual loss will be determined by the type of CNV and available treatment under the UK health service. Currently, the anti-VEGF medications may have a role in future management of acute SMH and occult CNV. Treatment with anti-VEGF and tPA/SF<sub>6</sub> may be a promising strategy for the special case only-eye patient with 6/60 vision and acute SMH (Cases 2 and 4). Following pneumatic displacement of SMH, intravitreal ranibizumab may be given during the first week postoperatively.

## CONCLUSIONS

The results of our clinical experience provide evidence that intravitreal tPA and SF<sub>6</sub> gas with face-down posturing is a safe and effective procedure for acute SMH. The optimal patient group would be those with acute SMH of less than 1 week's duration. In current practice within the UK, patients with AMD with SMH who have predominantly classic CNV can be sequentially treated with favorable visual outcomes. The technique is minimally invasive, and its role in combination with anti-VEGF agents for all types of CNV presenting with acute SMH needs to be explored.

*None of the authors has any proprietary interest in any of the products named in this article.*

Reprint requests to:  
 Mahiul M.K. Muqit, MD  
 Department of Ophthalmology  
 Bradford Teaching Hospitals  
 NHS Foundation Trust  
 Duckworth Lane, Bradford, BD96RJ UK  
 mmmk3@aol.com

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