

Pneumatic displacement of submacular haemorrhage



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Abstract

Purpose: To evaluate the outcomes of pneumatic displacement of submacular hemorrhage secondary to choroidal neovascular membrane (CNV) ($n = 9$) and retinal arterial macroaneurysm (RAM) ($n = 3$).

Methods: This is a retrospective case series study of 12 eyes from 12 patients in Aberdeen Royal Infirmary, Aberdeen, UK. The mean duration of visual loss was 10.8 ± 4.11 days. All cases received intravitreal injection of expansile gas within 24 h of presentation (C3F8 in 11 cases and SF6 in one case) and postured face down for five days. Anterior chamber paracentesis was done right after gas injection. Intravitreal anti-VEGF was injected at the same time in cases with CNV. Further anti-VEGF injections were done in CNV cases as needed afterwards. Cases were followed up for 6 months.

Results: The submacular hemorrhage was successfully displaced from underneath the fovea in all but one case. The bleeding disappeared totally in 44% of cases and was inferiorly displaced in 56%. VA improvement at 6 months was statistically significantly higher than baseline VA. All cases but 2 (one because of subfoveal fibrosis and one because of late presentation) experienced improved VA. The mean VA improved from 1.37 ± 0.18 logMAR at baseline to 0.83 ± 0.26 logMAR at 6 months. No complication related to the procedure was reported.

Conclusion: Pneumatic displacement of submacular hemorrhage appears to be a safe and effective technique to treat the condition. It is an easy procedure that can be done in outpatient setting. Further studies are needed to validate our results.

Keywords: Pneumatic displacement, Submacular hemorrhage, Retinal arterial macroaneurysm, CNV, Exudative AMD

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Introduction

Submacular haemorrhages (SMH) are associated with a variety of conditions including age-related macular degeneration (AMD), retinal artery macroaneurysm (RAM), ocular trauma, pathological myopia and presumed ocular histoplasmosis syndrome (POHS).^{1,2} Retrospective reports of the natural history of SMH demonstrated poor prognosis. Without treatment, SMH usually end up with poor final vision.³ This is due to retinal damage from the haemorrhage itself, which

is toxic to the photoreceptors. The layer of blood also acts as a diffusion barrier, impairing nutrient diffusion between the retinal pigment epithelium (RPE) and choroid as well as the photoreceptors.¹ Bennett et al. found that patients with fovea-involving SMH secondary to AMD had a mean visual acuity of 20/1700 at final follow-up with observation.⁴

The intervention for SMH can be done using vitrectomizing techniques or non-vitrectomizing techniques. Vitrectomizing techniques usually involve doing Pars-Plana vitrectomy (PPV) with intravitreal or subretinal injection of

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recombinant tissue-Plasminogen activator (rt-PA) to liquefy clotted blood and facilitate displacement with gas tamponade. Several case series reported successful displacement of the SMH (secondary to exudative AMD) and significant VA improvement with vitrectomizing techniques.⁵⁻⁷ In non-vitrectomizing techniques intravitreal expansile gases are injected to displace the SMH from underneath the fovea with or without other adjuvants. Heriot first described a simple technique for managing SMH by combined intravitreal injection of tissue plasminogen activator (t-PA) with expansile gas to pneumatically displace SMH.⁸ This technique reported a high anatomic success rate with few complications. Following that, other case series showed favourable outcomes using intravitreal t-PA in addition to expansile gases to displace SMH secondary to exudative AMD.^{9,10} Kitagawa and colleagues¹¹ recently published their positive results of using intravitreal injections of rt-PA, perfluoropropane (C3F8) and ranibizumab mainly in cases of polypoidal choroidal vasculopathy (PCV). They achieved total displacement of the SMH in 85% of cases ($n = 20$) and partial displacement in 15% of cases with significant VA improvement. However, they had vitreous haemorrhage or retinal detachment in 20% of cases that needed additional surgical intervention. De Jong and co-workers recently compared the outcomes of PPV, subretinal rt-PA, C3F8 and bevacizumab to intravitreal injection of rt-PA, C3F8 and bevacizumab in cases of SMH secondary to exudative AMD. The authors found no difference between the 2 groups.¹²

In cases of SMH related to RAM, some case series studies reported successful displacement of the SMH and VA improvement with PPV + subretinal t-PA injection and gas tamponade.^{13,14} However, several complications were reported with this technique including recurrence of SMH, vitreous haemorrhage, macular holes, retinal detachment, and hyphema requiring further interventions to address them. Some case series studies reported successful displacement of SMH with Intravitreal injection of t-PA and expansile gas.¹⁵ Mizutani et al. reported 100% recurrence of haemorrhage following intravitreal injection of t-PA and gas in cases of SMH secondary to RAM ($n = 4$) and recurrence of haemorrhage in 10% of cases treated with intravitreal gas only ($n = 10$). Based on this the authors did not recommend the use of intravitreal t-PA in SMH secondary to RAM.¹⁰

In this retrospective case series study we present the efficacy, safety, and visual outcomes of pneumatic displacement of SMH in cases of CNV and RAM without the use of rt-PA.

Methods

This study is a retrospective review of 12 consecutive patients who underwent intravitreal injection of expansile gas for pneumatic displacement of SMH, from 2009 to 2013 at Aberdeen Royal Infirmary, Scotland, UK. Each patient had a complete ophthalmological examination at initial presentation, which included visual acuity (VA), slit lamp biomicroscopy, fundus examination and Goldmann applanation

Table 1. Patients' data, causative pathology, gas used, and VA change.

Patient no.	Age (years)	Gender	Time from onset of symptoms to treatment (days)	Cause of haemorrhage	Gas used	Time to first FU (weeks)	Visual acuity (logMAR)			
							Initial presentation	1st follow-up	3 months	6 months
1	92	M	7	AMD	C3F8	4	1.6	0.48	0.3	0.1
2	89	F	0	AMD	C3F8	6	2	0.9	1	0.9
3	79	F	15	RAM	C3F8	4	0.9	0.7	0.6	0.6
4	95	F	28	AMD	C3F8	8	2.3	2.3	2	1.78
5	80	F	5	AMD	C3F8	6	2	2.8	2.8	2.8
6	86	F	1	AMD	C3F8	3	1	0.78	0.48	0.70
7	87	F	0	AMD	C3F8	2	2	2	0.3	0.3
8	89	F	3	RAM	C3F8	6	2	0.7	0.78	0.48
9	79	F	0	AMD	C3F8	5	0.6	0.48	0.4	0.3
10	85	F	42	AMD	C3F8	5	1	0.9	0.6	0.15
11	63	M	1	Inflammatory CNV	SF6	4	0.78	0.6	0.48	0.48
12	83	F	28	RAM	C3F8	4	1.18	1	1	1.18

M = Male. F = Female. AMD = age-related macular degeneration. RAM = retinal arterial macroaneurysm. CNV = choroidal neovascular membrane. FU = follow-up.

Table 2. Anti-VEGF use in the study.

Patient no.	Concurrent anti-VEGF injection	Anti-VEGF used	Prior anti-VEGF treatment	No of injections prior to haemorrhage	No of injections 6 months post-haemorrhage
1	Yes	Ranibizumab	No	0	6
2	Yes	Ranibizumab	No	0	3
3	No	None	No	0	0
4	Yes	Bevacizumab	No	0	2
5	Yes	Ranibizumab	Yes	12	1
6	Yes	Ranibizumab	No	0	4
7	Yes	Ranibizumab	No	0	3
8	No	None	No	0	0
9	Yes	Ranibizumab	No	0	4
10	Yes	Ranibizumab	No	0	3
11	Yes	Bevacizumab	Yes	1	4
12	No	None	No	0	0

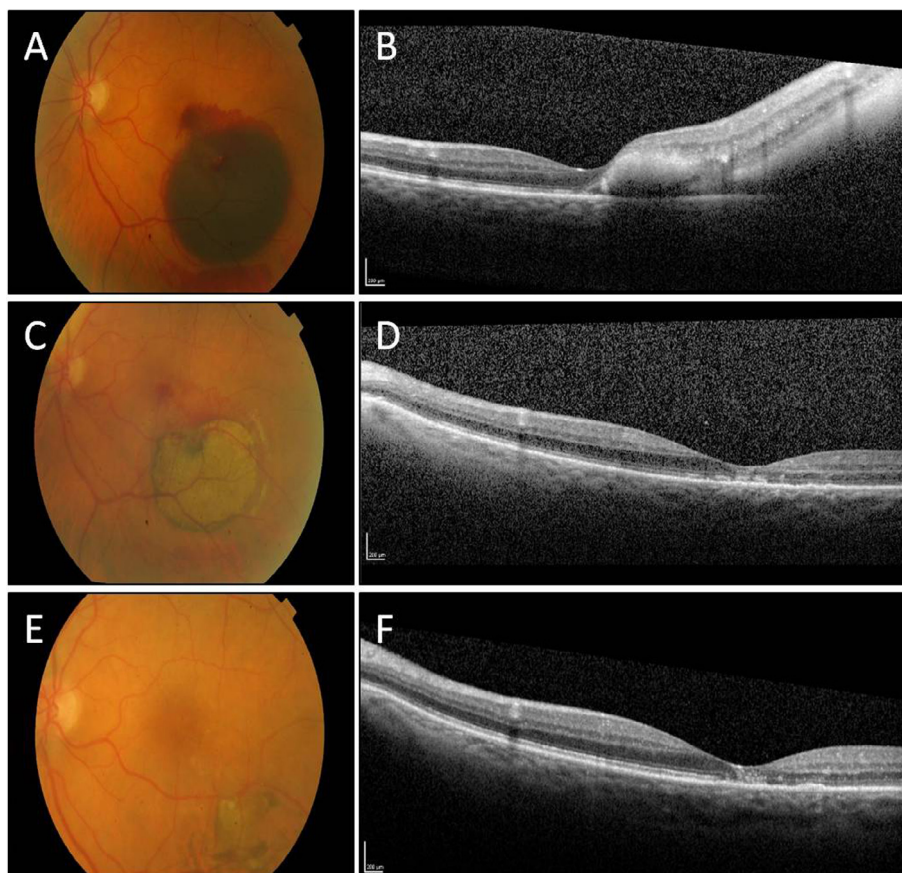


Figure 1. Colour fundus photographs and OCT images of a case of SMH secondary to RAM successfully treated with intravitreal gas injection. (A) Colour photograph at presentation. (B) OCT at presentation. (C) Colour photograph at 1 month follow-up. (D) OCT at one month follow-up. (E) Colour photograph at 6 months. (F) OCT at 6 months.

tonometry. Each patient was consented prior to intravitreal injection. Where available, fundus fluorescein angiography (FFA), optical coherence tomography (OCT) and colour fundus photograph (CFP) images pre- and post-procedure were analysed. All procedures were done in an outpatient setting with topical anaesthesia. The bulbar conjunctiva was cleaned and prepared using povidone-iodine to ensure aseptic conditions. 0.3 ml of 100% perfluoropropane gas (C3F8) or sulphur hexafluoride (SF6) gas was injected intravitreally using a 30 gauge needle 3.5 mm from the limbus in pseudophakic and 4 mm from the limbus in phakic eyes. In cases where choroidal neovascularisation (CNV) was the cause of the haemorrhage, ranibizumab or bevacizumab was also injected intra-vitreally at the same time. Anterior chamber paracentesis was done in all cases. Optic disc perfusion was checked after gas injection in all cases. Intra-ocular pressures were checked before and after the procedure. Patients were then advised to maintain face down positioning for five days.

Follow-up data were obtained for all patients at first follow-up (usually around one month), at 3 months and at 6 months after the procedure. Where OCT images were available, central retinal thickness (CRT) was measured at initial presentation and follow-up. The area of haemorrhage and degree of displacement were measured on CFP. VA obtained using Snellen was converted to logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Statistical analysis was performed using an IBM SPSS Statistics 22 and Microsoft Excel 2013. Paired Student's *t*-test

was used to analyse pre- and post-injection data. A *p*-value of less than 0.05 was considered to be significant.

Results

12 eyes of 12 patients (two males and ten females) with fovea-involving SMH were included in this study. Table 1 summarizes the data that were collected from each patient. The mean patients' age was 83.9 ± 2.39 years (range 63–95 years). The causes of the SMH were neovascular AMD ($n = 8$), retinal artery macroaneurysm ($n = 3$) and inflammatory CNV ($n = 1$) secondary to serpiginous choroidopathy. Intravitreal gas injection was performed in all patients by an experienced medical retina specialist within 24 h of presentation. All but one patient (patient 10) received 0.3 ml pure perfluoropropane (100% C3F8). One case received 0.3 ml pure sulphur hexafluoride (100% SF6).

The mean duration between onset of symptoms and treatment was 10.8 ± 4.11 days (range 0–42 days). Mean presenting visual acuity was 1.37 ± 0.18 (range 0.6–2.3 logMAR). The time to first follow-up differed among the patients seen and is dependent on the ophthalmologist who performed the procedure. Mean time to first follow-up was 4.8 ± 0.46 weeks (range 2–8 weeks).

Visual acuity improvement was seen in 83.3% ($n = 10$) of patients. One of the 2 patients with no VA improvement was noted to have advanced AMD with subfoveal fibrosis. Her visual VA was 2.0 logMAR at presentation and

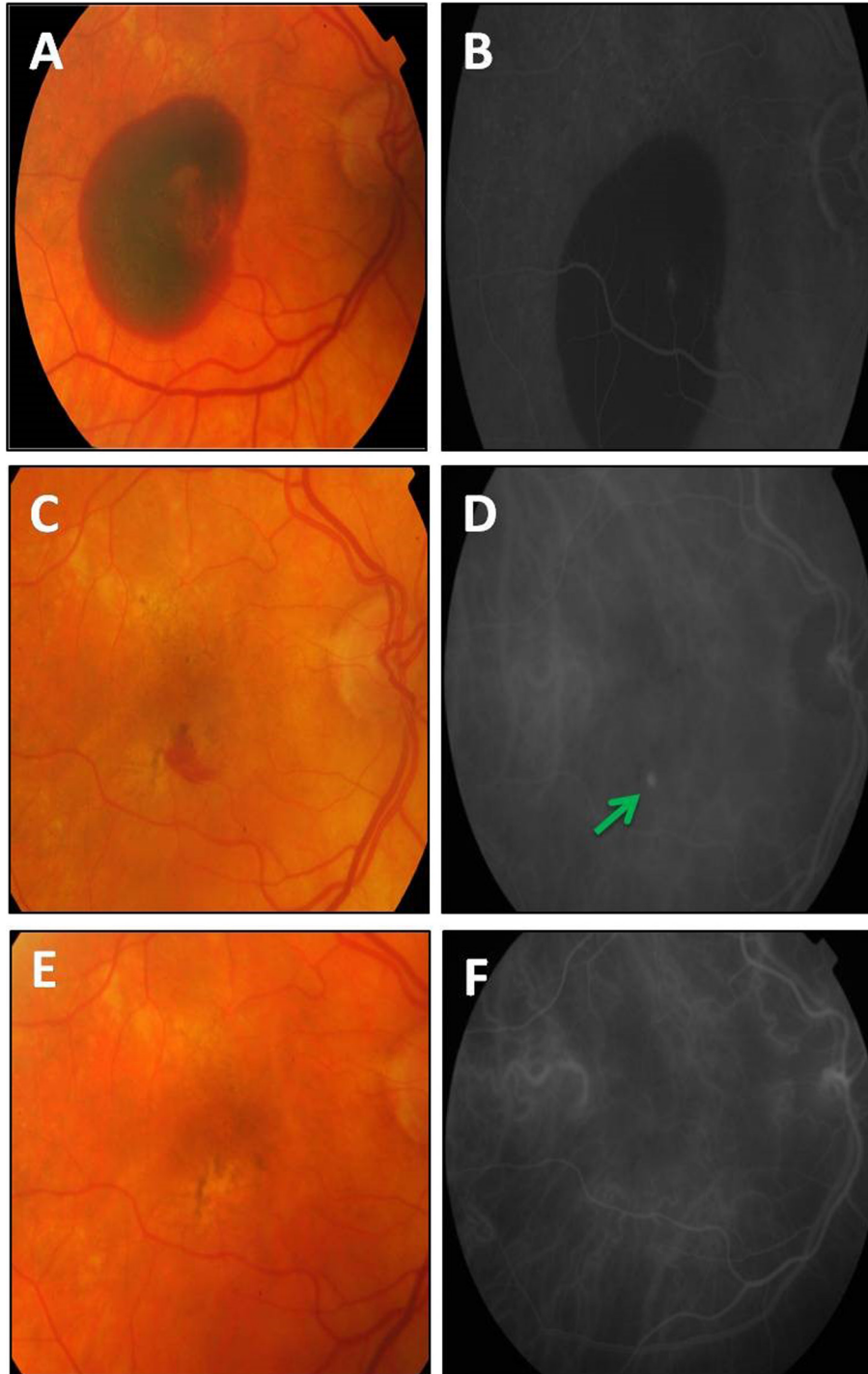


Figure 2. Colour photographs and angiography of a case of SMH secondary to exudative AMD successfully treated with intravitreal C3F8 injection + Lucentis injections. (A) Colour photograph at baseline. (B) FFA at baseline. (C) Colour photographs at 3 months follow-up (post gas and 3 lucentis injections). (D) ICG at 3 months showing a small residual hyperfluorescent spot due to RAP lesion (arrow). (E) Colour photograph at 6 months showing complete resolution of the lesion. (F) ICG at 6 months showing no residual hyperfluorescence.

2.8 logMAR at 6 months follow-up. No further treatment was recommended for that eye because of the irreversible foveal structural damage. The other case with no VA improvement presented with a prolonged history of blurred vision (over 4 weeks) and a very thick SMH and central macular thickness of 1148 μm on OCT. Her VA in the affected eye 1.18 logMAR at presentation and remained the same at 6 months follow-up with partial inferior displacement of SMH.

Mean visual acuity at first follow-up, at 3 months and at 6 months post-injection was 1.14 ± 0.22 logMAR, 0.92 ± 0.25 logMAR and 0.83 ± 0.26 logMAR respectively. When compared to visual acuity at initial presentation, the improvement at first follow-up was not statistically significant ($p = 0.14$). However, vision continued to improve and was statistically significant at 3 months ($p = 0.02$) and at 6 months post-injection ($p = 0.02$).

Of the 12 patients included in this series, 9 received intravitreal injections of anti-vascular endothelial growth factors (anti-VEGF) at the same time as pneumatic injection. Two of the patients had previous anti-VEGF injections for prior CNV. Further details of the anti-VEGF therapy are shown in Table 2. 75% ($n=9$) of patients had CFP taken at initial presentation. In this group of patients, mean haemorrhage area before pneumatic displacement was measured at $20.42 \pm 7.29 \text{ mm}^2$ (range 3.9–75.1 mm^2). The haemorrhage completely resolved in 44% ($n=4$) and inferior displacement of the haemorrhage with foveal clearing were achieved in the remaining 56% of patients at 3 months follow-up ($n=5$). Initial OCT images were obtained for 50% ($n=6$) of patients. Mean CRT at presentation was $573 \pm 128 \mu\text{m}$ (range 221–1148 μm). At 6 months post-injection, mean CRT was $196 \pm 23 \mu\text{m}$ (range 110–299 μm). This was found to be statistically significant ($p < 0.01$, Student's *T*-test). Fig. 1 shows pre and post injection appearance of one of our RAM cases. Fig. 2 shows the results of our technique in a case of SMH secondary to retinal angiomatous proliferation (RAP). In the later case (presented in Fig. 2) vision improved from CF at baseline to 6/7.5 at last follow-up.

There were no complications reported immediately post-surgery or during follow-up in any of the patients included in this study.

Discussion

SMH is associated with poor visual prognosis due to several different mechanisms including direct toxicity from the haemorrhage, mechanical traction on the photoreceptors and the establishment of a barrier effect between the photoreceptors and retinal pigment epithelium (RPE). Toxicity from the haemorrhage is caused by iron, in the form of ferritin, which is produced during hemolysis of the bleeding. Iron toxicity induces destruction of the photoreceptor and RPE layers. The traction effect on the photoreceptors is due to fibrin strands which forms within the haemorrhage during the clot retraction process. The layer of blood present also acts as a diffusion barrier preventing effective interchange of nutrients and metabolic by-products between the choroidal circulation and the retina. These three different mechanisms are time-specific and thus contribute to worsening visual prognosis with increasing duration of SMH.¹ Thus, displacement of the haemorrhage is recommended as soon as possible to reduce damage to the macular photoreceptors and improve the visual outcome.

In our retrospective study, we demonstrate successful displacement of SMH and significant improvement in vision with intravitreal injection of expansile gas. Anti-VEGF injection was also injected in cases of exudative AMD. The technique is a minimally invasive procedure that can be performed without delay in an outpatient setting where a clean intravitreal injection room is available. It seems to be a safe procedure with no complications detected in any of our patients. It is also a very cost-effective procedure. The potential complications that could happen with pneumatic displacement of SMH are similar to any intravitreal injection. No high IOP was detected in any of our cases post injection but this required paracentesis to be performed in all cases after gas injection.

Vitreotomizing techniques for SMH involve PPV, which is an expensive and time-consuming procedure that usually requires admission to hospital. PPV also needs to be done in operating theatre with special equipment as well as physician and nursing expertise. Moreover, PPV is associated with complications including cataract progression. In addition, vitrectomized eyes have short half-life of anti-VEGF drugs that are usually needed for further management in exudative AMD cases.¹⁶

Non-vitreotomizing techniques with intravitreal t-PA and gas injection are outpatient-based and simpler compared to PPV procedures. However, t-PA can cause adverse effects. Vitreous haemorrhage and rebleeding have been documented following the intravitreal use of t-PA in SMH cases.^{10,17} Hesse et al.¹⁸ also reported the occurrence of an inferior exudative retinal detachments in all patients injected with high doses of tPA (100 μg) which resorbed spontaneously after two weeks. Furthermore, experimental studies on animal eyes showed retinal toxicity of intravitreal t-PA injection.^{19,20}

Pneumatic displacement of SMH seems to be an easy and effective way of treatment of this devastating condition. Its success depends on many factors including the duration of bleeding (the shorter the duration, the better the results), level of haemorrhage (high success in subretinal haemorrhage rather than deeper bleedings), and patient compliance to posture face down for a few days.

Limitations of our study include its retrospective nature, and hence the absence of fixed protocols for imaging and follow-up of cases. There were also a small number of cases included in the study.

In conclusion, pneumatic displacement of SMH offers a safe and effective treatment option of SMH. It is a simple technique that can be delivered in outpatient clinic settings. Further studies are needed to validate the efficacy of this technique and compare its efficacy and cost-effectiveness with other techniques such as vitrectomy.

Conflict of interest

The authors declare that there are no conflict of interests.

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