

Visual Outcomes After Pneumatic Displacement for Submacular Hemorrhage Secondary to Neovascular Age-Related Macular Degeneration and Polypoidal Choroidal Vasculopathy

Krytha Tor¹, Remy Tor¹, Bottomalen Sorn¹, Guechlaing Chea¹, Leakhena Or¹, Papavarin Sirikietsoong², Navapol Kanchanaranya²

¹Ophthalmology Department, Preah Ang Duong Hospital, Phnom Penh, Cambodia

²Ophthalmology Department, Thammasat University Hospital, Pathum Thani, Thailand

Abstract: *This retrospective study evaluated the visual outcomes following pneumatic displacement for submacular hemorrhage secondary to neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. Twenty-four patients presenting within 15 days of symptom onset with submacular hemorrhage measuring 2 to ≥ 6 disc diameters underwent intravitreal injection of 100% perfluoropropane gas (0.2 to 0.4 mL). Anti-VEGF therapy was administered after confirmation of the underlying etiology using angiographic imaging. Successful displacement of hemorrhage from the fovea was achieved in 85% of evaluable cases. At 6 months, visual acuity improved in 78.3% of patients, and 43.5% gained at least two lines of vision. Mild vitreous hemorrhage was the most common complication. Visual prognosis appeared to be associated with hemorrhage size, displacement success, macular scarring, and response to anti-VEGF therapy. Pneumatic displacement may be a useful treatment option for selected patients with recent submacular hemorrhage.*

Keywords: submacular hemorrhage; pneumatic displacement; neovascular age-related macular degeneration, polypoidal choroidal vasculopathy; anti-VEGF; visual outcome

1. Introduction

Submacular hemorrhage (SMH) is a serious complication of exudative age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV) that leads to severe and irreversible damage to the photoreceptors and outer nuclear layer [1,2]. SMH results in an acute and severe decrease of vision, especially if the blood clot is thick and the fovea is involved [3,4,5]. Retrospective reports of the natural history of submacular hemorrhage demonstrated poor prognosis. Without treatment, SMH usually ends up with poor final vision [6]. This is due to retinal damage from the hemorrhage 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 [7]. The treatment strategies for submacular hemorrhage include: (I) displacement of blood from the fovea, usually by injection of an expansile gas; (II) pharmacologic clot lysis such as with rtPA; and (III) treatment of the underlying choroidal neovascularization (CNV) or PCV, such as with anti-VEGF agents. Displacement of SMH away from the fovea with an expansile gas was first described by Heriot in 1996 [8], and is the mainstay for any technique that attempts to displace subretinal blood.

Since then, anti-VEGF has revolutionized treatment of neovascular AMD and its action could potentially be enhanced by the displacement of thick SMH from underlying CNV membranes or PCV [9]. Ohji et al [10] demonstrated an 80%

complete displacement rate in eyes with SMH treated with pneumatic displacement within 6 days of onset. A study comparing anti-VEGF monotherapy with the combination therapy of anti-VEGF + pneumatic displacement reported more rapid reduction of central foveal thickness and faster visual improvement in the combination therapy group at one-month post treatment, but no difference was found between the groups at six months [11].

2. Methods

This study was designed as a retrospective. 24 patients who were diagnosed with sub-macular hemorrhage and underwent intravitreal injection of expansible gas for pneumatic displacement in the ophthalmology department of Thammasat Hospital University, Thailand, from 23rd January 2013 to 23rd December 2019. This study was approved by The Human Ethics Committee of Thammasat University with declaration of Helsinki number 161/2020. The patients were selected from 48 SMH who received pneumatic displacement in the same period. 24 SMH were excluded from the study due to 3 patients were diagnosed as pathologic myopia, 2 patients were retinal artery microaneurysm and 19 patients were incomplete documents. Each subject had a complete ophthalmological examination at initial presentation, which included visual acuity (VA), slit lamp biomicroscopy, fundus examination and airpuff tonometry. Informed consent was obtained from each patient prior to intravitreal injection. Where available, fundus fluorescein angiography (FFA), indocyanine green angiographic (ICGA), optical coherence tomography (OCT) and color fundus

photograph (CFP) images pre and post-procedure were analyzed.

Inclusion criteria were the presence of a large submacular hemorrhage with a size 2-disc diameters and ≥ 6 -disc diameters (divided into 2 groups 2-5 DD and ≥ 6 DD) located in the macular region and a duration of symptoms < 15 days.

Exclusion criteria included: presence of choroidal neovascularization secondary to pathologic myopia, or retinal artery macroaneurysm; tears of the retinal pigment epithelium (RPE); and other maculopathies, such as diabetic maculopathy or retinal vascular occlusion.

Table 1: Demographic data for patients with sub-macular hemorrhage

Patients	Group 2-5 DD (n = 16)	Group ≥ 6 DD (n = 8)	Total (n = 24)
Gender, n (%)			
Women	6 (37.5)	5 (62.5)	11 (45.83)
Men	10 (62.5)	3 (37.5)	13 (54.16)
Mean Age (years)			63.66 \pm 7.71
Onset of symptoms (days)			5.9 \pm 1.76
Laterality, n (%)			
Left	9 (56.25)	4 (50)	13 (54.16)
Right	7 (43.75)	4 (50)	11 (45.83)
Lens status			
Pseudophakia	7 (43.75)	1 (12.5)	8 (33.33)
Phakia	9 (56.25)	7 (87.5)	16 (66.66)
Causes			
AMD	7 (43.75)	3 (37.5)	10 (41.66)
PCV	9 (56.25)	4 (50)	13 (54.16)
Unidentified	0	1 (12.5)	1 (4.16)

DD: Disc Diameter, AMD: Age related Macular Degeneration, PCV: Polypoidal Choroidal Vasculopathy

All procedures were done in an outpatient or operation room with topical anesthesia. The bulbar conjunctiva was cleaned and prepared using povidone-iodine to ensure aseptic conditions. 0.2 - 0.4 ml of 100% perfluoropropane gas (C3F8) was injected into the vitreous to displace the sub-macular hemorrhage using a 30-gauge needle 3.5 mm from the limbus in pseudophakic and 4 mm from the limbus in phakic eyes. An anterior chamber paracentesis 0.05 - 0.1 ml was done immediately in all patients. Intra-ocular pressures were checked after the procedure by digital pressure. All patients were instructed to maintain a prone position. For safety, all patients were admitted for 1 day before discharge from hospital. After the expansile gas was completely absorbed, FFA and ICGA were performed to find the cause of the hemorrhage. After that, in cases where PCV or neovascular AMD were the cause of the hemorrhage, bevacizumab, ranibizumab or aflibercept was injected into patients' vitreous.

Follow-up data were obtained from all patients at first follow-up (usually around one month), at 3 months and at 6 months after the procedure. Central foveal thickness (CFT) was measured at initial presentation and follow-up by optical coherence tomography (Spectral Domain OCT, Carl Zeiss Cirrus 4000 HD-OCT). The diameter of the SMH was measured

on the color fundus photographs or clinical estimation on slit lamp biomicroscopy as disc diameters by investigators. The degree of blood displacement was determined by comparing fundus photographs or documents taken before and 1 month after the procedure. Complete displacement was defined as no blood or only a thin layer of blood within one-disc area of the fovea. The indications and procedures for additional treatment were as follows. First, was the presence of a rhegmatogenous retinal detachment (RRD) with vitreous hemorrhage or dense vitreous hemorrhage, and these were treated by pars plana vitrectomy (PPV). Second, neovascular AMD or PCV was the cause of sub-macular hemorrhage confirmed by investigator decision (History of the patient, ophthalmological examination, OCT of macular, FA or ICG) and these were treated by anti-VEGF therapy (Intravitreal bevacizumab, ranibizumab or aflibercept). Recurrence of SMH, vitreous hemorrhage, macular holes, retinal detachment, endophthalmitis and high intra-ocular pressure were noted in all cases. For statistical analysis, VA was converted to logarithm of the minimum angle of resolution (logMAR). All statistical data were analyzed using an IBM SPSS version 23 and recorded using Microsoft Excel 2013. Paired student's t-test was used to compare pre- and post-injection data. A *p*-value of less than 0.05 was considered to be significant.

3. Results

Among 48 patients diagnosed as sub-macular hemorrhage during the study period, only 24 patients met the inclusion criteria. They were divided into two groups depending on the size of the hemorrhage: 2-5 disc diameters (n = 16) and ≥ 6 disc diameters (n = 8). Demographic data of the study patients is demonstrated in Table 1. The mean age was 63.66 \pm 7.71 years old ranged from 55-83 years old. In all participants, 33.33% or 8 patients were pseudophakia. The causes of SMH were neovascular AMD (n = 10), PCV (n = 13) and unidentified (n = 1). The mean onset of the symptoms and treatment of the disease was 5.9 \pm 1.76 days (range from 3-10 days).

23 patients (95.83%) had completed visual acuity. The mean baseline of visual acuity was 1.34 \pm 0.58 logMAR (range 0.4-2.7 logMAR). The mean visual acuity at the first month of follow-up, at 3 month and at 6 month post-injection was 1.33 \pm 0.61 logMAR, 0.87 \pm 0.43 logMAR and 0.80 \pm 0.41 logMAR respectively. When compared to visual acuity at initial presentation, the improvement at first follow-up was not statistically significant (*p* = 0.5). However, the visual acuity at 3 month and 6 month post-injection improved significantly with *p*-value of 0.002 and < 0.001 . At 6 months, Visual acuity improvement was seen in 78.26% (n = 18) of patients. 20 patients (86.95%) had final visual acuity equal to or better than 1.00 logMAR. 10 patients (43.47%) were gained visual acuity ≥ 2 lines. Two of the five patients with no visual acuity improvement were noted with active disease (loss of visual acuity at least five letters with OCT evidence of fluid in the macular) treating with multiple intravitreal anti-VEGF and presented with geographic atrophy and subfoveal fibrosis from AMD. Last, three of five patients were presented with macular scar from PCV.

According to the Table 2, the mean visual acuity at 1 month follow-up showed no statistically significant difference despite different size of hemorrhage, lens status of patients or the cause of SMH. In different size of hemorrhage group; however, the mean visual acuity improved significantly at 3 month and 6 month follow-up ($p=0.02$, $p<0.001$) if the size was 2-5 disc diameters. If the hemorrhage size was larger or equal to 6-disc diameters, the improvement of visual acuity was significant only at 6 month follow-up ($p=0.004$). In addition, there was no change in visual acuity in pseudophakic patients in all follow-

up visits. It was because of the macular scar formation in 50% of pseudophakic patients. On the other hand, phakic patients had improvement in the visual acuity at 3 month follow-up and 6 months follow-up with $p=0.001$ and $p<0.001$. Last but not least, PCV, which is a cause of SMH, demonstrated significant improvement in visual acuity at both 3 month and 6 month visits while the cause of AMD didn't have visual acuity improvement until 6 month visits.

Table 2: Visual acuity outcome

	Visual acuity (logMAR)			
	Initial presentation	1 month follow-up	3 months follow-up	6 months follow-up
All participants	1.34 ± 0.58	1.34 ± 0.62 <i>0.5</i>	0.87 ± 0.43 <i>0.002</i>	0.8 ± 0.41 <i>< 0.001</i>
SMH of 2-5 DD	1.26 ± 0.57	1.18 ± 0.56 <i>0.35</i>	0.80 ± 0.30 <i>0.003</i>	0.76 ± 0.26 <i>0.001</i>
SMH ≥ 6DD	1.48 ± 0.61	1.62 ± 0.64 <i>0.35</i>	1.01 ± 0.60 <i>0.10</i>	0.87 ± 0.62 <i>0.004</i>
Pseudophakia	1.18 ± 0.49	1.42 ± 0.70 <i>0.24</i>	1.05 ± 0.59 <i>0.27</i>	0.98 ± 0.46 <i>0.17</i>
Phakia	1.42 ± 0.62	1.29 ± 0.58 <i>0.24</i>	0.78 ± 0.30 <i>0.001</i>	0.70 ± 0.35 <i>< 0.001</i>
AMD	1.41 ± 0.65	1.46 ± 0.60 <i>0.41</i>	0.98 ± 0.36 <i>0.05</i>	0.80 ± 0.36 <i>0.01</i>
PCV	1.23 ± 0.53	1.26 ± 0.65 <i>0.44</i>	0.82 ± 0.47 <i>0.02</i>	0.84 ± 0.45 <i>0.02</i>

SMH: Sub-macular Hemorrhage, AMD: Age related Macular Degeneration, PCV: Polypoidal Choroidal Vasculopathy

20 of 24 patients had completed the location of displacement. The submacular hemorrhage was successfully displaced from underneath the fovea in all except 3 cases (15%). 12 of 20 cases (60%) were inferiorly displaced, 4 of 20 cases (20%) were superiorly displaced and 1 of 20 case (5%) was temporally displaced. 3 patients of non-displacement of submacular hemorrhage were documented with visual acuity less than 1.00 logMAR.

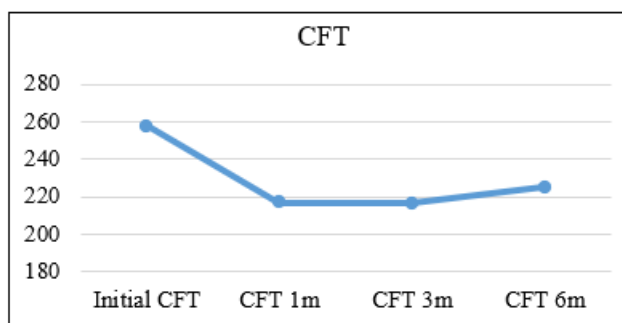
Of the 24 patients in this study, 20 patients received intravitreal injections of anti-VEGF after expandable gas was totally absorbed and confirmed the cause as PCV or AMD by FFA or ICGA. Further details of the anti-VEGF therapy are shown in Table 3. Most of the patients received anti-VEGF therapy at 3 month follow up. The mean injection of intravitreal anti-VEGF after completely reabsorption expandable gas was 2.41 ± 0.69 . Two of the patients had previous anti-VEGF injections for prior CNV and another one for PCV.

Table 3: Anti-VEGF use in the study

Patients No.	Concurrent anti-VEGF injection	Anti-VEGF used	Prior anti-VEGF treatment	No of injections prior to hemorrhage	No of injections 6 months post-hemorrhage
1	Yes	Avastin	No		2
2	Yes	Aflibercept	Yes	3 Lucentis	2
3	Yes	Avastin	No		2
4	Yes	Aflibercept	No		1
5	Yes	Avastin	No		1
6	Yes	Avastin	No		3
7	Yes	Lucentis	No		2
8	Yes	Aflibercept	No		3
9	No		PDT		
10	Yes	Avastin	No		2
11	Yes	Avastin	No		3 (PDT 1)
12	Yes	Aflibercept	No		3
13	Yes	Aflibercept	No		3
14	No				
15	Yes	Avastin	No		3
16	No		No		
17	Yes	Aflibercept	No		3
18	Yes	Aflibercept	Yes	5 Aflibercept	3
19	Yes	Aflibercept	No		2

20	Yes	Avastin	Yes	2 Aflibercept	3
21	Yes	Aflibercept	No		2
22	No		No		
23	Yes	Avastin	No		3
24	Yes	Aflibercept	No		3

The mean central fovea thickness (CFT) at initial presentation was $257.67 \pm 86.84 \mu\text{m}$ (range 111–449 μm). When compared to the initial thickness, the improvement at first follow-up was statistically significant with the mean value of $217 \pm 44.30 \mu\text{m}$ ($p = 0.002$) and continued to maintain until 3 months and 6 months of follow up at the mean of $216.41 \pm 44.30 \mu\text{m}$ and $224.72 \pm 66.54 \mu\text{m}$ respectively ($p = 0.01$ and $p = 0.04$) (Graph 4).



Graph 4: Central fovea thickness in the study

CFT: Central Foveal Thickness

4. Safety

Over the 6 month study period, after pneumatic displacement and anterior chamber paracentesis 0.05-0.1 ml in all patients, there was no complication documented in high intra-ocular pressure. Vitreous hemorrhage was noted in 10 patients (41.66%), among which, 8 cases (33.33%) were mild and 2 cases (8.33%) were severe underwent pars plana vitrectomy. Vitreous hemorrhage was observed in 1 eye after 5 days, 1 eye after 6 days, 3 eyes after 7 days, 3 eyes after 1 month and 2 eyes after 2 months. VH was reported in the same number in both 2-5 disc diameter and ≥ 6 disc diameter size of hemorrhage group which was 5 and 5 respectively.

2 patients (8.33%) were found with rhegmatogenous retinal detachment which needed pars plana vitrectomy. 1 patient (4.16%) was observed with macular hole and 1 patient (4.16%) was reported with recurrence hemorrhage (Table 5).

Table 5: Complications of pneumatic displacement

Complication	2-5 DD (n = 16)	≥ 6 DD (n = 8)	Total (n = 24)
VH	5	5	10 (41.66%)
RRD	2	0	2 (8.33%)
MH	0	1	1 (4.16%)
Recurrence	0	1	1 (4.16%)
Endophthalmitis	0	0	0
High IOP	0	0	0

VH: Vitreous Hemorrhage, RRD: Rhegmatogenous Retinal Detachment, MH: Macular Hole

5. Discussion

The purpose of this study was to evaluate the visual prognosis and safety of pneumatic displacement in patients with submacular hemorrhage secondary to neovascular AMD and PCV. In this retrospective study, 78.26% of patients showed visual improvement at the 6-month follow-up, comparable to the 83.3% improvement reported by Abdelkader et al [12]. Additionally, 43.47% of patients gained two or more lines of visual acuity, which is consistent with previous studies reporting improvement rates ranging from 45.5% to 67% after pneumatic displacement with rt-PA and gas [13], [15].

In our study, visual outcomes were not significantly different between procedures performed with or without rt-PA. This finding raises questions regarding the additional benefit of rt-PA, particularly in light of its potential retinal toxicity. Hesse et al [13] reported retinal toxicity, including exudative retinal detachment and electroretinographic changes, following intravitreal rt-PA injections at doses of 100 μg . Experimental studies by Johnson et al [16] and Hrach et al [17] also demonstrated dose-dependent retinal toxicity and recommended avoiding doses greater than 25 μg .

Because of these concerns, several studies have evaluated pneumatic displacement using gas alone. Ohji et al [10] reported successful displacement or reduction of hemorrhage in all treated eyes, while Gopalakrishan et al [18] observed complete or partial displacement in 16 of 20 patients, with visual improvement in 70% of cases. Similar to previous reports, visual recovery in our study was limited in some patients because of subfoveal fibrosis, thick hemorrhage, choroidal neovascular scarring, or progression of AMD [12], [14], [15], [18].

Early intervention may contribute to better outcomes. All patients in our study presented within two weeks of symptom onset, and 43.47% achieved an improvement of at least two lines of visual acuity. Hattenbach et al [14] similarly reported favorable outcomes in patients treated within two weeks. We also found that smaller hemorrhages (2–5 disc diameters) were associated with greater visual improvement, consistent with findings from Hassan et al [15] and Schulze et al [19]. In addition, hemorrhage thickness appeared to influence final visual acuity more strongly than hemorrhage area. Glatt and Machemer [1] proposed that subretinal blood damages photoreceptors by impairing metabolic exchange between the retinal pigment epithelium and choroid.

Complete displacement of blood from the fovea was another important predictor of visual recovery. In our series, 85% of patients achieved complete displacement, and most obtained visual acuity of 1.00 logMAR or better. Guthoff et al [20] also

demonstrated significantly better outcomes when blood was completely displaced from the fovea.

The natural course of submacular hemorrhage is generally associated with poor visual prognosis, particularly in AMD [3], [18], [21]. Gass et al [23] suggested that hemorrhage beneath the retinal pigment epithelium and progressive neovascular scarring contribute to poorer outcomes in AMD compared with PCV. This may explain why visual improvement in the AMD group was slower than in the PCV group during early follow-up period. However, with adjunctive anti-VEGF therapy, visual acuity improved in most patients by 6 months.

The major complication in our study was vitreous hemorrhage, occurring in 33.33% of patients. Most cases were mild, although two patients with PCV required vitrectomy for dense vitreous hemorrhage. Similar complication rates have been reported previously [14], [18], [22].

This study has several limitations, including its retrospective design, short follow-up duration, small sample size, and lack of a control group. Important variables, such as hemorrhage thickness and displacement distance, were not consistently documented. In addition, only patients with early-onset SMH were included.

In conclusion, pneumatic displacement with expansile gas appears to be a feasible and relatively safe treatment option for selected patients with recent submacular hemorrhage secondary to neovascular AMD or PCV. Visual outcomes may be influenced by hemorrhage size, successful displacement from the fovea, macular scarring, and response to subsequent anti-VEGF therapy. Larger prospective controlled studies with longer follow-up are needed to further validate these findings.

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