

Combined Pharmacological and Pneumatic Displacement Therapy for Sub-Macular Haemorrhage Secondary to Age-Related Macular Degeneration: A Case Series and Review of the Literature

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Case Report

Combined Pharmacological and Pneumatic Displacement Therapy for Sub-Macular Haemorrhage Secondary to Age-Related Macular Degeneration: A Case Series and Review of the Literature

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Abstract

Purpose: To present the clinical outcomes of a combined pharmacological and gas-assisted treatment approach for sub-macular haemorrhage secondary to neovascular age-related macular degeneration (nAMD). **Methods:** A retrospective analysis was conducted on ten patients with sub-macular haemorrhage secondary to nAMD treated between 2024 and 2025. Each patient received a single intravitreal injection of tissue plasminogen activator (tPA; alteplase, Actylise 10, Boehringer Ingelheim, Int.) and perfluoropropane (C₃F₈, Micromed) gas. This treatment was administered within 3 weeks of symptom onset (range 7-60 days). Subsequently, all patients received anti-VEGF injections of aflibercept (Eylea 2mg, or Eylea 8 mg, Bayer) using a treat-and-extend (T&Ex) regimen, started 7–14 days after the tPA + gas injection. Clinical evaluation included best-corrected visual acuity (BCVA), fundus photography, optical coherence tomography (OCT), and OCT- angiography angio-OCT at baseline and at 7 -14 days, 1 month, 3 months, and 6 months after the initial tPA + gas injection. **Results:** All patients showed rapid anatomical improvement of the haemorrhage. Visual acuity improved in the majority of cases, with an average gain of three ETDRS lines at four weeks, an additional three lines at three months, and over four lines at six months. No major adverse events were reported. One patient developed a transient intraocular-pressure rise, which was easily controlled with medication. **Conclusion:** Prompt combined therapy using intravitreal alteplase with C₃F₈ gas, followed by anti-VEGF treatment, may offer a safe and minimally invasive alternative to surgery for sub-macular haemorrhage due to nAMD, providing promising visual and anatomical outcomes.

Keywords: sub-macular haemorrhage; neovascular age-related macular degeneration (nAMD); tissue plasminogen activator (alteplase); expansile gas; anti-VEGF

1. Introduction

Sub-macular haemorrhage is a vision-threatening complication of neovascular age-related macular degeneration (AMD); (Figure 1), polypoidal choroidal vasculopathy, and rupture of macular macro- or micro-aneurysms [1,2].

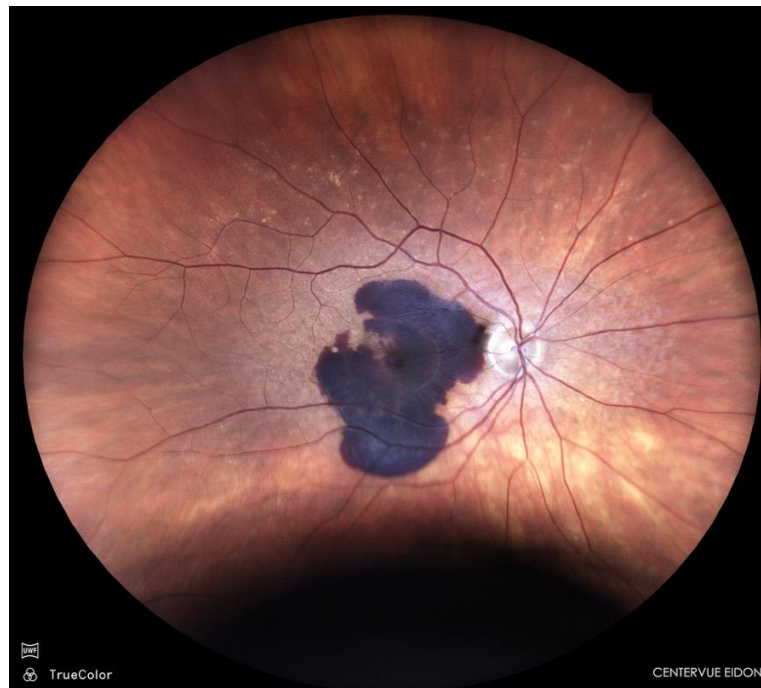


Figure 1. Sub-macular haemorrhage in AMD.

The accumulation of blood in the subretinal space exerts toxic and mechanical effects on the photoreceptors and retinal pigment epithelium, often leading to irreversible vision loss if left untreated [3–5]. The presence of iron, haemosiderin, and fibrin within the subretinal space triggers photoreceptor apoptosis within hours, emphasising the need for early displacement of the clot to restore the foveal architecture and prevent permanent macular damage [6].

Current therapeutic options include enzymatic clot liquefaction with tissue plasminogen activator (tPA; alteplase) with or without pneumatic displacement using expansile gas (e.g. sulphur hexafluoride [SF_6] or perfluoropropane [C_3F_8]), anti-VEGF therapy alone, and surgical interventions such as pars plana vitrectomy with subretinal injection of tPA. [7–12] While surgery can be effective, it carries higher risks and costs and may not be accessible in all clinical settings [8,9,11].

A combined pharmacological and pneumatic approach allows both enzymatic degradation of the subretinal clot and mechanical displacement of blood from the foveal region. This strategy can be performed in an outpatient setting and offers a favourable balance between efficacy, safety, and accessibility—particularly for elderly patients who, owing to comorbidities such as cardiovascular disease, hypertension, or diabetes, are often unfit for surgery [12].

Aim

This article presents a case series illustrating the efficacy of a combined minimally invasive approach for sub-macular haemorrhage—intravitreal tPA with expansile gas (C_3F_8)—followed by adjuvant anti-VEGF therapy within a treat-and-extend (T&Ex) regimen. The aim is to evaluate the anatomical and functional outcomes achieved with this combined management strategy in patients with sub-macular haemorrhage secondary to nAMD over a six-month follow-up period.

2. Materials and Methods

Study Design and Participants:

This retrospective case series included ten patients (10 eyes) treated in 2024 and 2025 at the Prof. Zagórski Eye Surgery Centre, Nowy Sącz, Poland. All patients presented with a diagnosis of sub-macular haemorrhage secondary to exudative AMD.

Inclusion criteria were as follows: a diagnosis of neovascular AMD with sub-macular haemorrhage confirmed by OCT and fundus imaging, and symptom onset within 60 days prior to treatment.

Exclusion criteria consisted of haemorrhage lasting longer than two months or the presence of scarring.

All procedures were conducted in accordance with institutional guidelines and the Declaration of Helsinki. Informed consent was obtained from all participants.

Treatment Protocol:

All patients underwent intravitreal injection of tPA (Alteplase, Actilyse® 100 µg/0.1 mL) combined with pure perfluoropropane gas (C₃F₈) 0.3 mL at 100% concentration, followed by anterior chamber paracentesis to prevent a rise in intraocular pressure (IOP). The procedure was performed under aseptic conditions in the operating theatre. After treatment, patients were instructed to maintain a prone position for at least three days to facilitate displacement of sub-macular blood.

Between 7 and 14 days after the initial tPA + gas injection, all patients began anti-VEGF therapy with either aflibercept 2.0 mg/0.1 mL (Eylea 2 mg, Bayer) or aflibercept 8 mg/0.1 mL (Eylea 8 mg, Bayer) using a treat-and-extend (T&Ex) regimen. The loading phase for both formulations consisted of three-monthly injections, followed by extension according to the T&Ex protocol.

Outcome Measures:

Patients underwent comprehensive ophthalmic evaluation at baseline and at 7 days or 14 days, 1 month, 3 months, and 6 months initial tPA and gas injection. Assessments included best-corrected visual acuity (BCVA) measured using an ETDRS chart, fundus photography, macular spectral-domain optical coherence tomography (SD-OCT), and optical coherence tomography angiography (OCT-A) at each time point.

3. Results

Ten patients (ten eyes) with sub-macular haemorrhage secondary to neovascular AMD were included. The mean age was 76.0 ± 6.1 years (range: 60–90 years). Five patients (50%) were female and five (50%) male. All eyes presented with fovea-involving haemorrhage. The mean duration from symptom onset to treatment was 25 ± 18 days (range: 7–60 days). Table 1 summarises the demographic data, diagnosis, and symptom onset.

Table 1. Demographic data with diagnosis and the onset of symptoms.

Case No	Age (y)	Sex	Initial diagnosis	Duration of symptoms (days)
1.	90	F	Sub-macular haemorrhage, AMD	60
2.	85	F	Sub-macular haemorrhage, AMD	7
3.	74	M	Sub-macular haemorrhage, AMD	21
4.	78	M	Sub-macular haemorrhage, AMD	10
5.	78	M	Sub-macular haemorrhage, AMD	7
6.	68	M	Sub-macular haemorrhage, AMD	14
7.	73	M	Sub-macular haemorrhage, AMD	7

8.	77	F	Sub-macular haemorrhage, AMD	56
9.	60	F	Sub-macular haemorrhage, AMD	60
10.	77	F	Sub-macular haemorrhage, AMD	8
mean	76			24
median	77			12

The mean baseline BCVA was 0.99 ± 0.21 logMAR (Snellen equivalent $\approx 20/180$). By 7–14 days, the mean BCVA improved to 0.89 ± 0.20 logMAR ($\approx 20/155$), representing an early gain of approximately one ETDRS line. At 1 month, the mean BCVA improved further to 0.80 ± 0.20 logMAR ($\approx 20/110$), corresponding to an average gain of two ETDRS lines. At 3 months, the mean BCVA reached 0.60 ± 0.18 logMAR ($\approx 20/80$), and by 6 months, it improved to 0.53 ± 0.20 logMAR ($\approx 20/70$), with six eyes (60%) gaining four or more ETDRS lines and none lost vision. Mean and median ETDRS line gains are shown in Figure 2, and BCVA changes over time are detailed in Table 2.

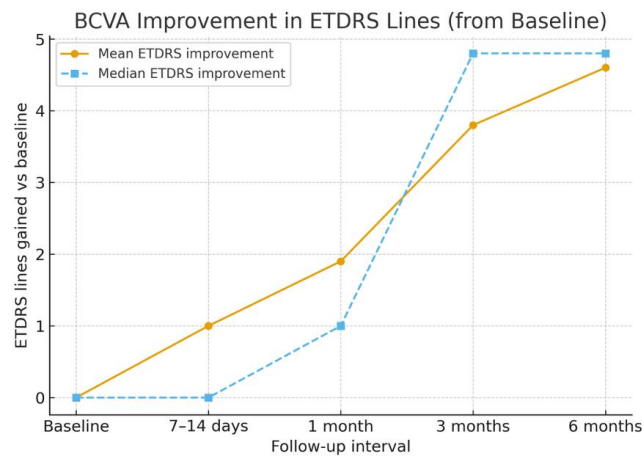


Figure 2. Mean and median EDTRS lines gain with time.

Table 2. BCVA change with time (logMAR).

Case No	BCVA Before	7–14 days postop.	1 month postop.	3 months postop.	6 months postop.	Complications
1	1.00	0.70	1.00	0.52	0.52	none
2	1.30	0.70	0.70	0.52	0.40	none
3	2.00	2.00	2.00	1.40	1.40	MNV scar
4	1.30	1.30	0.52	0.40	0.30	none
5	0.30	0.52	0.52	0.40	0.40	none
6	0.60	0.60	0.60	0.52	0.22	none
7	0.40	0.40	0.52	0.52	0.52	cataract

8	1.00	1.00	0.70	0.52	0.52	cataract
9	0.70	0.40	0.30	0.22	0.10	IOP rise
10	1.30	1.30	1.10	1.10	1.10	MNV scar
Mean	0.99	0.89	0.8	0.6	0.53	
Median	1.0	0.7	0.65	0.52	0.4	

Fundus photography and OCT imaging confirmed near-complete displacement of the haemorrhage by day 30 and restoration of the foveal contour in eight eyes (80%) as depicted in Figure 3, whereas two eyes (20%) showed residual ellipsoid-zone disruption and subsequent fibrotic scarring and atrophy, which is shown in Figure 4.

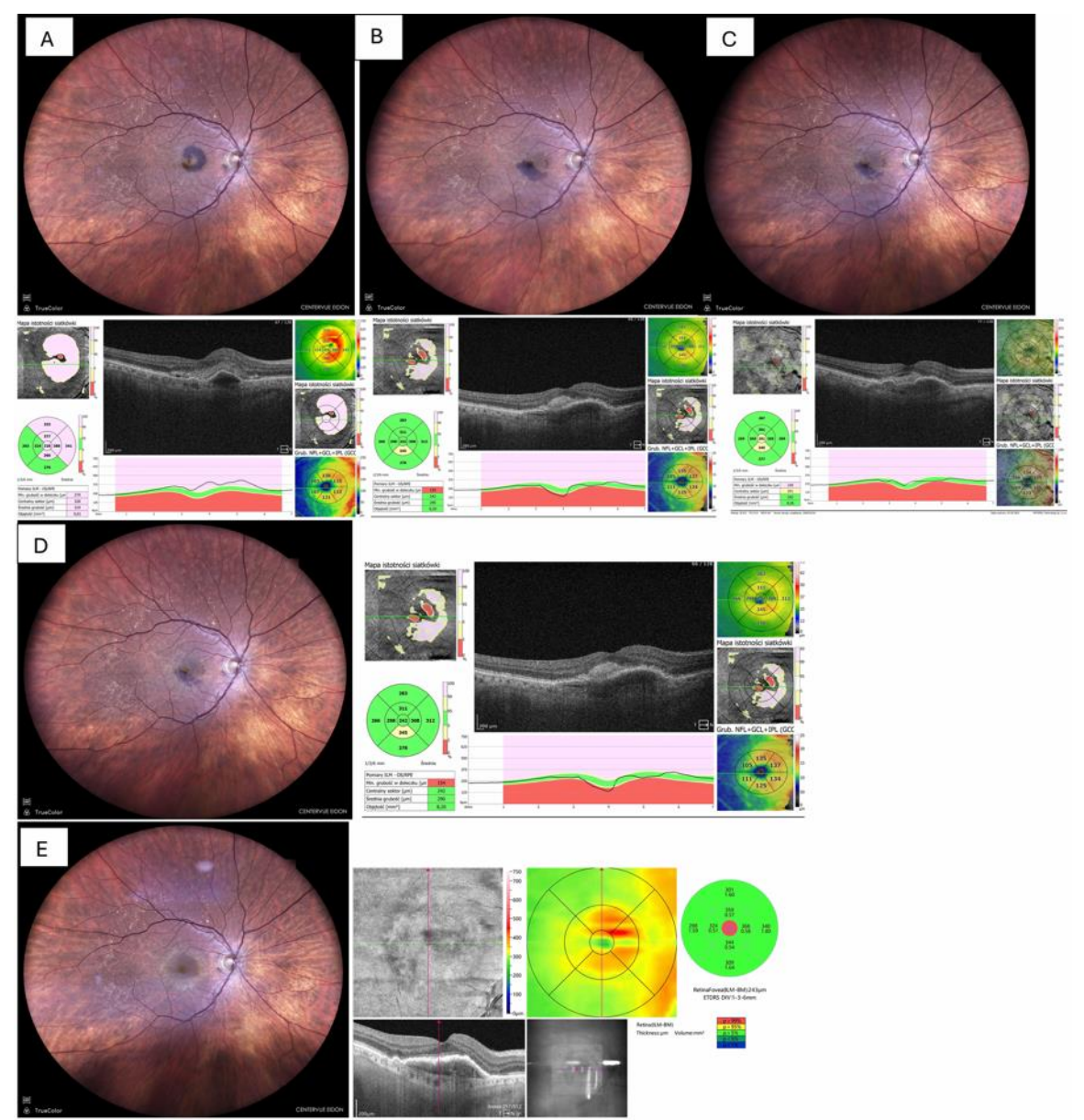


Figure 3. Resolution of hemorrhage with restoration of foveal contour. Figure legend: A. Fundus photo and OCT before tPA + gas administration. B. Fundus photo and OCT 14 days after tPA + gas, showing significant reduction in haemorrhage and retinal thickness; the patient received the first intravitreal aflibercept 2 mg (Eylea

2 mg, Bayer). C. Fundus photo and OCT 1 month postoperatively (only small remnants of blood visible). D. Fundus photo and OCT 3 months postoperatively, patient on aflibercept 2 mg T&Ex regimen. E. Fundus photo and OCT 6 months postoperatively, no blood visible but MNV still active, requiring continuation of anti-VEGF therapy. Foveal contour preserved.

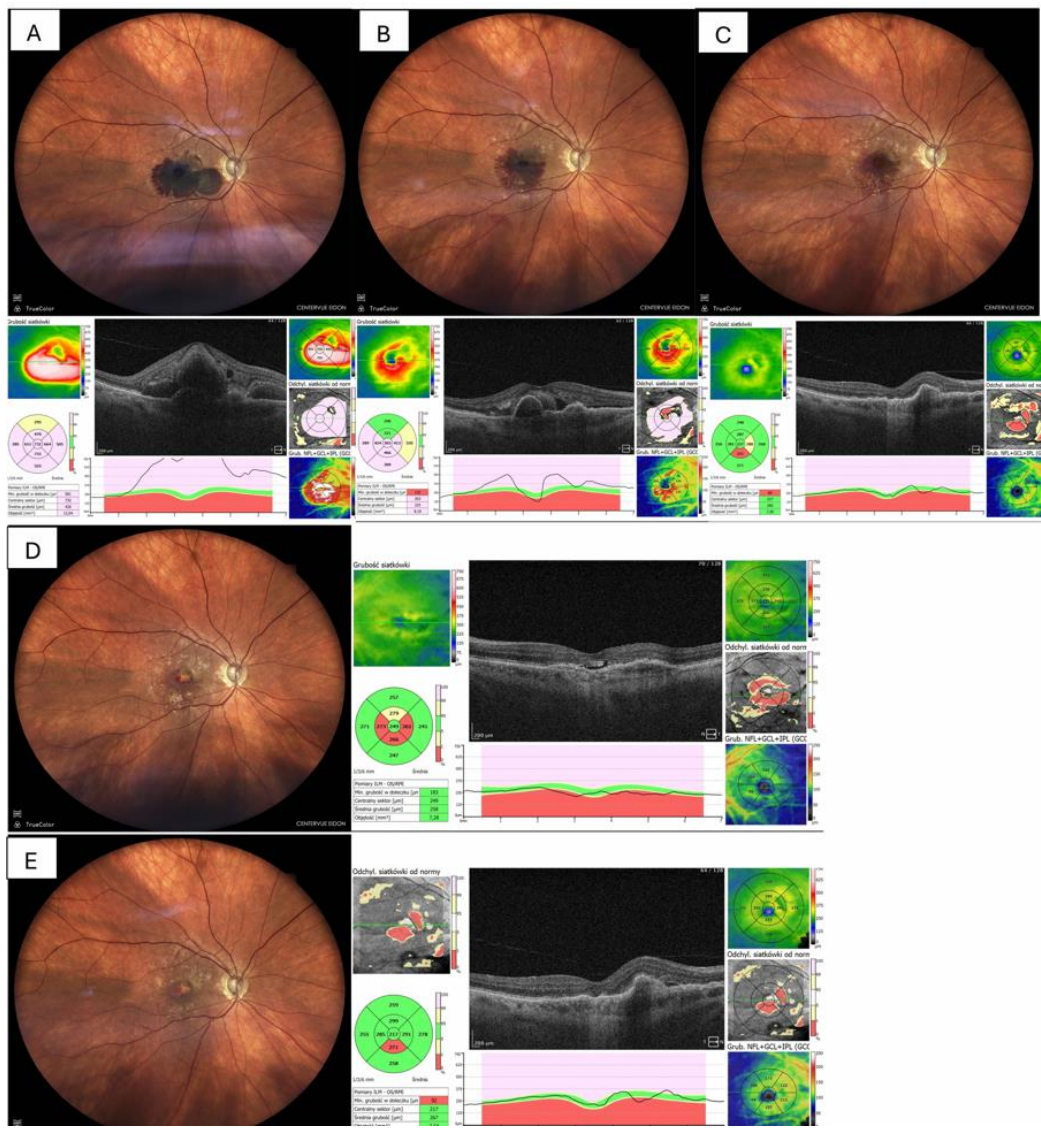


Figure 4. Resolution of haemorrhage with ellipsoid zone disruption. Figure legend: A. Fundus photo and OCT before tPA + gas, showing thick sub-macular haemorrhage involving the fovea. B. Fundus photo and OCT 7 days after tPA + gas, showing marked reduction of haemorrhage and retinal thickness; patient received first intravitreal aflibercept 8 mg (Eylea 8 mg, Bayer). C. Fundus photo and OCT 1 month postoperatively (thin blood remnants visible). D. Fundus photo and OCT 3 months postoperatively, showing foveal atrophy in both fundus image and OCT; patient on aflibercept 8 mg T&Ex regimen. E. Fundus photo and OCT 6 months postoperatively, no blood visible, with central atrophy and persistent MNV activity requiring ongoing anti-VEGF therapy.

Safety Outcomes:

One patient experienced a transient IOP rise (≥ 30 mmHg), which resolved following anterior-chamber paracentesis. Two patients developed cataract progression (non-vision-threatening), and two showed macular neovascularisation scarring.

No cases of endophthalmitis, retinal pigment epithelium (RPE) tear, retinal detachment, or recurrent haemorrhage occurred during the six-month follow-up.

Table 3 summarises the safety outcomes and complications.

Table 3. Safety outcomes and complications.

Finding	Reported	Case No
IOP rise	1 patient	Case 9
Cataract	2 cases	Cases 7 & 8
MNV scar	2 cases	Cases 3 & 10
Endophthalmitis/retinal detachment/other complications	None	None

4. Discussion

Sub-macular haemorrhage (SMH) in the context of neovascular AMD remains a pressing therapeutic challenge. Prompt, effective treatment is critical, as blood accumulation damages photoreceptors and the retinal pigment epithelium through mechanical separation, iron toxicity, and clot-related stress [4,5]. Early intervention is therefore vital to preserve macular integrity.

A 2024 meta-analysis revealed that combining tPA and anti-VEGF resulted in significant visual acuity improvement (−0.38 logMAR at 1 month, −0.47 logMAR at longer follow-up) with an 86% success rate in haemorrhage displacement [9]. Similarly, combining low-dose subretinal tPA with intravitreal anti-VEGF during vitrectomy produced favourable six-month outcomes, although retinal pigment epithelium (RPE) degeneration in some patients highlights the need for individualised treatment planning [3,10,13].

Notably, a recent randomised trial indicated that surgical management of SMH—vitrectomy with subretinal tPA and intravitreal gas—did not significantly outperform pneumatic displacement in improving visual outcomes. The ongoing TIGER trial is expected to provide clarity on surgical versus non-surgical strategies in large, fovea-involving haemorrhages [7,14]. Announced in 2020 and updated in 2025, this trial is still ongoing, with no results published yet [14,15].

Imaging evidence suggests that retinal damage depends more on the duration of haemorrhage than on the treatment technique, supporting the rationale for early combined therapy [11,16]. Although clinical practice varies—ranging from observation to monotherapy or combination therapy—our minimally invasive, simple yet effective protocol aligns well with the most evidence-supported approaches. Biologically, the basis for early treatment is compelling. Fibrin toxicity and photoreceptor separation were first demonstrated in animal models by Toth et al., while Lim et al. emphasised the risk of breakthrough haemorrhage and complications when triple therapy is delayed [4,13].

In summary, our findings complement the growing body of evidence supporting early, combined, minimally invasive pharmacological–pneumatic therapy for SMH secondary to AMD [9]. Going forward, randomised studies, extended follow-up, and image-guided treatment individualisation are needed to optimise outcomes.

Compared with classical surgical approaches (vitrectomy with sub-macular tPA), this method is less invasive, repeatable, and can be performed in an outpatient or office setting. Early initiation of treatment (preferably within 30 days) appears to be a critical factor in achieving favourable visual and anatomical results [3,10].

The main limitations of this study include its small sample size and retrospective, non-randomised design. Further prospective, randomised controlled trials are required to confirm our findings and to refine treatment timing and dosage protocols [15].

Conclusion

A combined treatment approach using a single intravitreal injection of alteplase with pure C₃F₈ gas, followed by anti-VEGF therapy within a treat-and-extend (T&Ex) regimen, can achieve significant visual and anatomical improvement in patients with sub-macular haemorrhage secondary

to AMD. Early intervention remains crucial, and this minimally invasive protocol may serve as a safe and effective alternative to more complex surgical procedures.

Funding: No external funding was received for this study.

Ethics: Statement: All procedures were conducted in accordance with institutional guidelines and the Declaration of Helsinki. Informed consent was obtained from all participants.

Conflicts of Interest: The authors declare no conflicts of interest related to this study.

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