Intravitreal r-tPA Injection and Pneumatic Displacement for Submacular Retinal Hemorrhage: A Case Series

Filippo Confalonieri\textsuperscript{a, b, c}, Ingar Stene-Johansen\textsuperscript{a}, Xhevat Lum\textsuperscript{a, d}, Goran Petrovski\textsuperscript{a, b, e}

\textsuperscript{a}Department of Ophthalmology, Oslo University Hospital, Oslo, Norway; \textsuperscript{b}Center for Eye Research, Department of Ophthalmology, Institute for Clinical Medicine, University of Oslo, Oslo, Norway; \textsuperscript{c}Department of Biomedical Sciences, Humanitas University, Milan, Italy; \textsuperscript{d}Eye Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia; \textsuperscript{e}Department of Ophthalmology, University of Split School of Medicine and University Hospital Centre, Split, Croatia

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Age-related macular degeneration · Subretinal macular hemorrhage · Vitreoretinal surgery · Subretinal r-tPA

Abstract
We describe the results of very early pars plana vitrectomy, subretinal r-tPA, and gas tamponade in patients with subretinal macular hemorrhage secondary to neovascular age-related macular degeneration. The patients ended up with a favorable functional recovery. We conclude that very early treatment might lead to a good functional prognosis.

Introduction
Retinal hemorrhages are some of the most common clinical signs in retinal disease and consist of a spectrum of blood collection differing in location, size, distribution, and etiology \cite{1}. Among subretinal hemorrhages, fovea-involving subretinal macular hemorrhage (SRMH) is a sight-threatening condition defined as blood collection between the neurosensory retina...
and the retinal-pigmented epithelium [2]. It can be caused by a plethora of eye conditions including neovascular age-related macular degeneration (n-AMD), pathologic myopia, polypoidal choroidal vasculopathy, rupture of retinal arterial macroaneurysms, presumed ocular histoplasmosis syndrome, and blunt trauma [3–7]. Without prompt treatment, visual prognosis is poor [8–10].

AMD is the leading cause of legal blindness in the industrialized world [11]. The real incidence of SRMH among patients with n-AMD is unknown [12], even though n-AMD has long been known to be a risk factor for submacular bleeding [8].

The scientific literature reports a wide range of possible procedures for SRMH, either stand-alone or combined, including vitrectomy, intravitreal recombinant tissue plasminogen activator (r-tPA) injection, subretinal r-tPA injection, subretinal BSS injection, air or gas endotamponade injection [13, 14]. In many circumstances, however, such interventions are not enough to improve visual acuity to that before SRMH, with chances for improvement being reduced the more delayed the intervention is performed [15–17].

Timing for administration of treatment has long been considered to be crucial [18]. Recently, the best final visual outcome has been reported when the duration of SRMH was less than 14 days, while no visual improvement was noticed when treatment was delayed by more than 21 days [19].

There is no consensus regarding treatment strategies, while the treatment technique is often determined by the dimension or duration of the hemorrhage and preference of the surgeon [20]. Since early photoreceptors’ damage has been reported as early as 24 h after SRMH [21, 22], we expect that an earlier treatment can provide a better functional outcome. To underpin the role of such an early treatment of SRMH, we hereby report 3 cases of prompt PPV, subretinal r-tPA injection, and gas tamponade for dense SRMH.

**Case Report**

**Case 1**

An 80-year-old woman with known n-AMD presented to the Department of Ophthalmology, Oslo University Hospital, Oslo, Norway, with a sudden decrease of vision and a central scotoma in the left eye soon after onset of symptoms, estimated as less than 24–48 h before. A hemorrhage was found at the fundus examination, so the patient was referred to the vitreoretinal section, where a dense SRMH was documented through fundus imaging (Fig. 1). The hemorrhage was 4-disc diameters on the largest meridian. Best corrected visual acuity in the left eye (Snellen chart) was 0.05 and intraocular pressure was 8 mm Hg. Optical coherence tomography scanning of the left eye showed a large SRMH (Fig. 2). The patient was operated on within 48–72 h from the diagnosis. PPV was performed under retrobulbar anesthesia. Subretinal injection of r-tPA (25 μg in 0.1 mL) in the inferotemporal quadrant was performed through a 41-gauge cannula. The vitreous cavity was filled with gas tamponade (20% SF6) after fluid/air exchange. The patient was instructed to maintain a prone position for 3 days postoperatively. The next day, the hemorrhage had started to move away from the fovea. BCVA improved to 0.5 by 5 weeks. Eleven weeks later, the patient underwent cataract surgery with IOL implantation in the capsular bag. A month after the cataract surgery, BCVA was 0.4 due to secondary macular edema and remained stable with intravitreal anti-VEGF treatment. Currently, AMD is stable with smaller size PED and slight fibrosis with intraretinal edema, which is now treated further with intravitreal injection of aflibercept. At the 5-week and 4-month control, the submacular hemorrhage had been successfully displaced out of the fovea (Fig. 3, 4). Despite the remaining n-AMD, the patient has not complained of any additional symptoms secondary to the SRMH.
Case 2

A 71-year-old man previously treated for n-AMD was referred to the Eye Hospital, Ljubljana, Slovenia, complaining of sudden decreased vision and central scotoma in his right eye after waking up that same day. BCVA in the right eye was counting fingers at 10 cm.

Fig. 1. a Preoperative fundus image of dense SRMH (left eye) and contralateral eye with dry AMD. b Same fundus images 4 months postoperatively.

Fig. 2. Preoperative OCT horizontal (upper) and vertical (lower) line scan of the macula. Large SRMH is evident in the left eye.
Ophthalmoscopy revealed dense SRMH involving the central fovea. The size of the hemorrhage was 4-disc diameters. The patient was operated on the next day and underwent PPV with subretinal r-tPA injection and gas tamponade (10% C3F8). At the 5-week and 4-month control, the submacular hemorrhage had been successfully displaced out of the fovea (Fig. 5), and, despite the remaining neovascular AMD, visual acuity remained stable at 0.25 (Snellen chart). The patient continued regular intravitreal anti-VEGF treatment in the postoperative period.

**Fig. 3.** One-month postoperative OCT horizontal (upper) and vertical (lower) line scan of the macula. Partial reabsorption of the SRMH is evident in the left eye.

**Fig. 4.** Four-month postoperative OCT horizontal (upper) and vertical (lower) line scan of the macula of the left eye showing further resolution of the SRMH and subretinal fluid.
Case 3

An 86-year-old man previously treated for n-AMD presented to the emergency section of the Eye Hospital, Ljubljana, Slovenia, complaining of a sudden decreased vision and central scotoma in his right eye soon after onset of symptoms, estimated as less than 24–48 h before. BCVA in the right eye was hand motion. A dense SRMH involving the macula was observed in the involved eye. The size of the hemorrhage was 5-disc diameters. The patient was operated on within 24 h from the diagnosis and underwent PPV with subretinal r-tPA injection and gas tamponade (10% C3F8). At the 5-week and 6-month control, the submacular hemorrhage had been successfully displaced out of the fovea (Fig. 6), and, despite the remaining n-AMD, visual acuity was stable at 0.16. The patient continued regular intravitreal anti-VEGF treatment.

Discussion

We report a case series of 3 patients with recent-onset SRMH that underwent PPV, subretinal r-tPA injection, and nonexpansile concentration of gas tamponade that resulted in an improved visual acuity. Dense SRMH is a common manifestation of neovascular AMD. It is associated with sudden visual loss, and the functional prognosis is often poor. The functional outcome may also be influenced by the duration and the size of submacular hemorrhage. Persistent SRMH damages the photoreceptors through three main mechanisms: iron-related toxicity, impairment of diffusion of oxygen and nutrition, and mechanical damage due to clot contraction [23–28].

The timing of treatment is believed to be crucial in resolving SRMH, and this is the reason why a prompt displacement of subretinal blood from the macula is supported by experts. Most of the studies carried out so far include patients with hemorrhage of ≤14 days, while older SRMH have been associated with significantly worse functional outcome [8, 18, 21, 23, 26, 29].

Recently, adverse prognostic factors have been identified as older age at diagnosis, higher SRMH elevation, and previous pro re nata intravitreal regime [17]. However, it is common that very seldom the patient presents early enough to be operated on within a few hours of
symptoms onset, so that in most recent studies, 14 days cut-off time from symptoms onset has been used as inclusion criterium in the studies. Moreover, very seldom has such a good functional improvement or outcome been reported [13, 14, 30, 31].

Our results are encouraging and underpin the role of timing in the treatment of SRMH. This case series can spur further research on the management of SRMH secondary to n-AMD and can shift the paradigm or approach to the disease into an ophthalmological emergency.

**Conclusion**

We hereby show through a small case series that very early PPV, subretinal r-tPA, and nonexpansile gas tamponade can lead to a favorable functional prognosis.

**Statement of Ethics**

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Ethical approval was not required for this study in accordance with local or national guidelines. Written informed consent was obtained from patients for publication of the details of their medical case and any accompanying images.

**Conflict of Interest Statement**

Filippo Confalonieri, Ingar Stene-Johansen, Xhevat Lumi, and Goran Petrovski have no conflicts of interest to declare.

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**Author Contributions**

Study conception and design and analysis and interpretation of results: Filippo Confalonieri, Xhevat Lumi, and Goran Petrovski; data collection: Filippo Confalonieri, Ingar Stene-Johansen, Xhevat Lumi, and Goran Petrovski; draft manuscript preparation: Filippo Confalonieri. Filippo Confalonieri, Ingar Stene-Johansen, Xhevat Lumi, and Goran Petrovski reviewed the results, approved the final version of the manuscript, and attest that they meet the current ICMJE criteria for authorship.

**Data Availability Statement**

All data generated and analyzed during this study are included in this published article. Further inquiries can be directed to the corresponding author.
References

1. Kanukollu VM, Ahmad SS. Retinal hemorrhage. StatPearls. StatPearls Publishing; 2022. [cited 2022 May 27]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560777/.

2. Shukla UV, Kaufman EJ. Intraocular hemorrhage. StatPearls. Treasure Island, FL: StatPearls Publishing; 2022. [cited 2022 May 27]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK560779/.

3. Ohji M, Saito Y, Hayashi A, Lewis JM, Tano Y. Pneumatic displacement of subretinal hemorrhage without tissue plasminogen activator. Arch Ophthalmol. 1998 Oct;116(10):1326–32.

4. Nayak S, Padhi TR, Basu S, Das T. Pneumatic displacement and intra-vitreal bevacizumab in management of sub-retinal and sub-retinal pigment epithelial hemorrhage at macula in polyoidal choroidal vasculopathy (PCV): rationale and outcome. Semin Ophthalmol. 2015 Jan;30(1):53–5.

5. Thuruthumaly C, Yee DC, Rao PK. Presumed ocular histoplasmosis. StatPearls. StatPearls Publishing; 2022. [cited 2022 May 27]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560777/.

6. Fleckenstein M, Keenan TDL, Guymer RH, Chakravarthy U, Schmitz-Valckenberg S, Klaver CC, et al. Age-related macular degeneration. Nat Rev Dis Primers. 2019 Dec;5:199–211.

7. Nakamura H, Hayakawa K, Sawaguchi S, Gaja T, Nakazawa M, Naito H. Retinal hemorrhage. StatPearls. Treasure Island, FL: StatPearls Publishing; 2022. [cited 2022 Jul 30]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560777/.

8. Stevens TS, Bressler NM, Maguire MG, Bressler SB, Fine SL, Alexander J, et al. Occult choroidal neovascularization in age-related macular degeneration. A natural history study. Arch Ophthalmol. 1997 Mar;115(3):345–50.

9. Bressler NM, Bressler SB, Childs AL, Haller JA, Hawkins BS, Lewis H, et al. Surgery for hemorrhagic choroidal neovascularization with submacular hemorrhage and without choroidal neovascularization. Retina. 2011 Jan;31(1):74–80.

10. Toth CA, Morse LS, Hjelmeland LM, Landers MB. Fibrin directs early retinal damage after experimental sub-retinal hemorrhage. Arch Ophthalmol. 1991 May;109(5):723–9.

11. Ali Said Y, Dewilde E, Stalmans P. Visual outcome after vitrectomy with subretinal tPA injection to treat subretinal hemorrhage and choroidal neovascularization in age-related macular degeneration: ophthalmic findings: SST report no. 13. Ophthalmology. 2004;111(11):1993–2003.

12. Fleckenstein M, Keenan TDL, Guymer RH, Chakravarthy U, Schmitz-Valckenberg S, Klaver CC, et al. Age-related macular degeneration. Nat Rev Dis Primers. 2021 May 6;7(1):31–25.

13. Pierre M, Mainguy A, Chatziralli I, Pakzad-Vaezi K, Ruiz-Medrano J, Bodaghi B, et al. Macular hemorrhage due to age-related macular degeneration or retinal arterial macroaneurysms. Graefes Arch Clin Exp Ophthalmol. 2008 May;246(5):661–9.

14. Thach T, Peng J, Lin BL, Chen C, Lee M, Lin S, et al. Visual outcome after vitrectomy in submacular hemorrhage. Ophthalmology. 2020 Sep 21;127(10):1390–6.

15. Steel DHW, Sandhu SS. Submacular haemorrhages associated with neovascular age-related macular degeneration. Br J Ophthalmol. 2011 Aug;95(8):1051–7.

16. de Silva SR, Bindra MS. Early treatment of acute submacular haemorrhage secondary to wet age-related macular degeneration: treatment outcomes and brief literature review. Int Ophthalmol. 2021 Dec;41(12):4037–46.

17. Kishikova L, Saad AAA, Vaideanu-Collins D, Isac M, Hamada D, El-Haig WM. Comparison between different techniques for treatment of submacular haemorrhage due to age-related macular degeneration. Eur J Ophthalmol. 2021 Sep;31(5):2621–4.

18. All Said Y, Dewilde E, Stalmans P. Visual outcome after vitrectomy with subretinal tPA injection to treat submacular hemorrhage secondary to age-related macular degeneration or macroaneurysm. J Ophthalmol. 2014;2014:621043:1–6.

19. Karamitsos A, Papastavrou V, Ivanova T, Cottrell D, Stannard K, Karachrysafi S, et al. Management of acute submacular hemorrhage using intravitreal tissue plasminogen activator, C3F8, and an anti-VEGF agent. Eye. 2016 Jul;30(7):952–7.

20. Peter M, Mainguy A, Chatziralli I, Pakzad-Vaezi K, Ruiz-Medrano J, Bodaghi B, et al. Macular hemorrhage due to age-related macular degeneration or retinal arterial macroaneurysms: predictive factors of surgical outcome. J Clin Med. 2021 Dec 10;10(24):5787.

21. Hattenbach LO, Klaas C, Koch FH, Gümbel HO. Intravitreous injection of tissue plasminogen activator and gas in the treatment of submacular hemorrhage under various conditions. Ophthalmology. 2001 Aug;108(8):1485–92.

22. Karamitsos A, Papastavrou V, Ivanova T, Cottrell D, Stannard K, Karachrysa S, et al. Management of acute submacular hemorrhage using intravitreal injection of tissue plasminogen activator and gas: a case series. SAGE Open Med Case Rep. 2020 Nov 18;8:2050313X20970337.

23. Yiou G, Mahmoud TH. Subretinal hemorrhage. Dev Ophthalmol. 2014;54:213–22.

24. Toth CA, Morse LS, Hjelmeland LM, Landers MB. Fibrin directs early retinal damage after experimental subretinal hemorrhage. Arch Ophthalmol. 1991 May;109(5):723–9.

25. de Silva SR, Bindra MS. Early treatment of acute submacular haemorrhage secondary to wet AMD using intravitreal tissue plasminogen activator, C3F8, and an anti-VEGF agent. Eye. 2016 Jul;30(7):952–7.

26. Forte M, Mainguy A, Chatziralli I, Pakzad-Vaezi K, Ruiz-Medrano J, Bodaghi B, et al. Macular hemorrhage due to age-related macular degeneration or retinal arterial macroaneurysms: predictive factors of surgical outcome. J Clin Med. 2021 Dec 10;10(24):5787.
27 Hassan AS, Johnson MW, Schneiderman TE, Regillo CD, Tornambe PE, Poliner LS, et al. Management of submacular hemorrhage with intravitreous tissue plasminogen activator injection and pneumatic displacement. *Ophthalmology*. 1999 Oct;106(10):1900–6; discussion 1906–7.

28 Balughatta P, Kadri V, Braganza S, Jayadev C, Mehta RA, Nakhate V, et al. Pneumatic displacement of limited traumatic submacular hemorrhage without tissue plasminogen activator: a case series. *Retin Cases Brief Rep.* 2019;13(1):34–8.

29 Bennett SR, Folk JC, Blodi CF, Klugman M. Factors prognostic of visual outcome in patients with subretinal hemorrhage. *Am J Ophthalmol*. 1990 Jan 15;109(1):33–7.

30 Iannetta D, De Maria M, Bolletta E, Mastrofilippo V, Moramarco A, Fontana L. Subretinal injection of recombinant tissue plasminogen activator and gas tamponade to displace acute submacular haemorrhages secondary to age-related macular degeneration. *Clin Ophthalmol*. 2021 Aug 28;15:3649–59.

31 Jackson TL, Bunce C, Desai R, Hillenkamp J, Lee CN, Lois N, et al. Vitrectomy, subretinal Tissue plasminogen activator and Intravitreal Gas for submacular haemorrhage secondary to Exudative age-Related macular degeneration (TIGER): study protocol for a phase 3, pan-European, two-group, non-commercial, active-control, observer-masked, superiority, randomised controlled surgical trial. *Trials*. 2022 Jan 31;23(1):99.