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Macular hemorrhage – therapy

Małgorzata Gawlak[1], Katarzyna Guzek[1], Bartosz Kuźlik[1], Ada Pandey[1], Dominika Prokop[1], Oliwia Cwalina[1], Kinga Czarnacka[1], Alicja Chmura-Hołyst[1], Isamel Alsoubie[1], Katarzyna Sajak-Hydzik[1, 2], Ilona Pawlicka[1, 2], Agnieszka Piskorz[1, 2], Maciej Kozak[1, 2], Anna Roszkowska[2]

[1] Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University
Dean: Prof. Filip Gołkowski, MD, PhD

[2] Clinical Department of Ophthalmology, Provincial Ophthalmological Hospital, Krakow
Head: Prof. Anna Roszkowska, MD, PhD

HIGHLIGHTS

Submacular hemorrhage in the macular area is an emergency condition in ophthalmology, threatening permanent loss or significant deterioration of vision, which is why it is so important to choose the appropriate and most effective therapeutic method.

ABSTRACT

Submacular hemorrhage treatment is still an important issue in ophthalmology. At present we lack algorithms of treatment that could be used in clinical practice. Efficacy of every treatment method seems to differ by individual factors simultaneously existing in each patient. Therefore, anti-VEGF agents remain crucial in treating patients with coexisting vasculopathy, while in posttraumatic hemorrhage we should lean towards other approaches, like pneumatic displacement. Operative methods, despite being more invasive and burdened with higher potential risk, are indispensable in large hemorrhages, significantly speeding up clot removal. The primary aim of this work is to collect recent data regarding this issue and to determine usefulness of treatment methods in specific cases, regarding factors such as hemorrhage pathophysiology. The following article pertains to currently used treatment methods, such as: pneumatic displacement, anti-VEGF therapy, rtPA and operative methods.

Key words: submacular hemorrhage, pneumatic displacement, anti-VEGF, rtPA, vitrectomy

INTRODUCTION

Subretinal hemorrhage is characterized by the accumulation of blood between the retinal pigment epithelium (RPE) and the neurosensory retina. It is a serious and vision-threatening complication of many conditions, the most common of which is the exudative form of age-related macular degeneration (AMD). Other causes include ocular trauma, retinal artery macroaneurysms, blood clotting disorders, macular neovascularization (MNV, macular neovascularization) of various etiologies, Terson's syndrome, iatrogenic hemorrhage during drainage of subretinal fluid during procedures on the detached retina or laser retinal photocoagulation and idiopathic bleeding [1]. Macular subretinal hemorrhage (SMH, submacular hemorrhage), in addition to its etiology, can also be classified based on the size of the hemorrhage, measured in disc diameter (DD). A distinction is made between SMH: small < 4 DD, medium – above 4 DD, but not exceeding the temporal vascular arcades, and large - extending beyond the aforementioned area [2]. The size of the stroke itself affects further treatment decisions and prognosis. Blood trapped in the subretinal space within a few hours can cause irreversible damage to the photoreceptors as a result of the toxic effects of iron, hemosiderin, fibrin and oxidative stress, as well as reduced metabolism (transport of oxygen, nutrients, metabolic by-products) and compression of the fibrin in the resulting clots. Hemorrhage can also be localized to the space beneath the retinal pigment epithelium, thus reducing visual acuity in cases of large pigment epithelial detachments or RPE ruptures. Risk factors for macular hemorrhage among general diseases include hypertension and chronic use of anticoagulants and antiplatelet drugs [1].

METHODS OF TREATMENT

Pneumatic displacement

A method of treating macular hemorrhage involving moving pooled blood away from the macula and involving the administration of fibrinolytic tissue plasminogen activator (tPA, tissue plasminogen activator) into the vitreous chamber, followed by air and gas: sulfur hexafluoride (SF6) or octafluoropropane (C3F8) was presented by Chen and associates. In the scheme, a fundus examination was carried out after the administration of pupil-dilating drops to check the perfusion of the central retinal artery, followed by paracentesis of the anterior chamber to prevent a spike in intraocular pressure. The next step was the intravitreal administration of tissue plasminogen activator, which, through its action of activating the conversion of plasminogen to plasmin, promotes fibrinolysis, i.e. clot dissolution, followed by an average of 0.2–0.5 ml of sulfur hexafluoride or octafluoropropane gas into the vitreous chamber. After the procedure, the patient should remain in a face-down position to facilitate the movement of blood from under the macula. It is important to keep in mind the possible toxic effects of TPA on the retina, which can lead to necrosis and loss of photoreceptors, so it is recommended to avoid using a dose of the product above 50 μg [3]. To compare the efficacy of using gas alone or together with TPA for acute subretinal hemorrhage caused by trauma and choroidal rupture, Holland et al. conducted a study on two patients. In one patient, gas alone (0.04 ml SF6) was injected, while in the other, the procedure was extended with the addition of 50 μg TPA. They found that in the patient treated with gas alone, visual acuity improved after 2 months to 20/32, where it was initially 20/100, while in the other patient, treated with VA (visual acuity) combination therapy, it improved from 20/125 to 20/63 after 6 days and 20/32 after 10 weeks. The researchers concluded that the VA improvement in both patients was similar, while the combination procedure could result in faster treatment effects [4]. Considering the possibility of toxic effects of tissue plasminogen activator, they began performing pneumatic blood transfer alone using only gas, after which the face-down position also had to be maintained. Gopalakrishan et al. conducted a study involving 20 patients with subretinal hemorrhage of various etiologies. The time between hemorrhage and treatment ranged from 1 to 30 days, and the baseline VA varied between hand movement in front of the eye and 20/125. They were treated with an intravitreal injection of gas, followed by supine positioning for 5 days to 7 days. In 16 patients, it was observed that the extravasated blood was completely or partially moved away from the macula within 7 days after the injection. In contrast, 4 patients developed hemorrhage into the vitreous, which required vitrectomy [5]. Ohji et al. also demonstrated that pneumatic blood gas displacement (C3F8) is an effective method of treating subretinal hemorrhage, without the need for tissue plasminogen activator. Ultimately, visual acuity improved in all subjects [6].

In a case series of three patients with subretinal hemorrhage caused by recent or old blunt trauma, Balughatta et al. used 0.3 ml of pure C3F8 and performed anterior chamber paracentesis, achieving significant displacement of SMH (submacular hemorrhage) and significant improvement in vision in 2 of the 3 cases described. The period from the onset of injury in the subjects ranged from 2 days to 2 weeks. Therefore, it has been concluded that pneumatic displacement of blood with gas is an effective technique in the management of patients after SMH caused by recent or old trauma [7]. The pneumatic displacement method is associated with a greater surgical burden than the intravitreal administration of TPA. Its efficacy appears to be related to the time elapsed from the onset of trauma

to the onset of treatment, but these speculations require further studies [8].

Anti-VEGF therapy

Intravitreal anti-VEGF therapy plays a particular role in treatment of SMH secondary to age-related macular degeneration (AMD) or polypoidal choroidal vasculopathy (PCV). This method is undeniably less invasive compared to other available surgical methods. Possible side effects include e.g.: short- or long-term increased intraocular pressure, appearance of vitreous floaters, conjunctive hemorrhage and ocular inflammation (estimated risk circa 0.05%) [9–11]. Vitreous body haemorrhages are a more frequent side-effect in patients currently on anticoagulative medication and in cases of large SMH > 20 DAs (disc areas) [12].

There are currently multiple similarly acting drugs available with varying pharmacokinetic parameters. No conclusive research exists as far as their efficacy in comparison to one another, although in situations where no desired clinical effect is observed, switching drugs may be beneficial [13, 14]. Studies based on animal models revealed that prior vitrectomy may change pharmacokinetics of intravitreal drugs like anti-VEGF by increasing their clearance and reducing the half-life. This may indicate altered treatment regimen in some patients, such as favouring long-acting drugs like broculizumab [15–17].

In SMH, anti-VEGF drugs are used both in mono- and combined therapy. Anti-VEGF monotherapy especially benefits patients with small, thin SMH and good to intermediate baseline BCVA (best corrected visual acuity). Larger haemorrhages that fail to meet aforementioned criteria, despite good long-term anti-VEGF monotherapy outcomes in some patients, appear to respond in a more positive manner to combined therapy with anti-VEGF drugs and pneumatic displacement or surgery [18–21]. It is possible that anti-VEGF drugs may find use in patients with SMH related to COVID-19 infections. Notably, a case study of a 25 y/o male infected with Covid-19 complicated with SMH, who showed BCVA improvement from 6/60 to 6/9 after treatment with ranibizumab in monotherapy [22]. There are no existing studies in regards to post-traumatic SMH treatment with anti-VEGF drugs; considering their broad spectrum of action, including anti-inflammatory capability, it is likely they could positively influence the treatments outcomes in such cases [23, 24].

Surgery and rtPA injections

Most studies on recent treatments for macular degeneration describe combination therapies. Treatment can take the form of monotherapy or combination therapy, which involves combining, for example, PPV (pars plana vitrectomy – posterior vitrectomy through the planar part of the ciliary body) with gas and/or rtPA (recombinant tissue plasminogen activator) depending on the presence or absence of vitreous hemorrhage. Some authors offer suggestions for approaching treatment planning from the pathophysiological side and argue that surgery is not indicated in every case [25]. An important element is the determination of the size of the hemorrhage what determines the approach to carry out surgery with classical methods, such as PPV, or a non-operative approach, such as the administration of rtPA. Treatments are chosen for large strokes and the need for faster removal but surgery alone without simultaneous administration of gas or e.g. rtPA may not achieve the desired results [26].

One cause of SMH is the exudative form of age-related macular degeneration (nAMD, neovascular age-related macular degeneration) and at this point there is no consensus on a uniform management of this pathogenesis. Two studies looking at different treatment strategies and different surgical techniques using PPV, found no statistically significant differences between treatments at the 12-month interval other than earlier improvement with anti-VEGF agent [27, 28]. One and the other group of investigators use BCVA as a determinant. A retrospective study by Ali Said et. al indicates that simultaneous administration of air and rtPA during PPV, for SMH, shows improvement in patients 6 weeks after the procedure but unfortunately visual acuity decreases as the underlying disease continues. This indicates that some procedures, despite SMH removal, will not ultimately lead to improved vision but only remove the clot[29]. Despite this, a study using rtPA and gas during PPV but using SF6 instead of air resulted in improved BCVA at 12 months and clot removal in 100% of patients [30].

However, PPV is still one of the primary surgical tools in the fight against macular hemorrhage. New types of mechanical intervention for SMH may be an alternative to PPV in the future. Yokoyama et al. in 2022 successfully used subretinal endoscopic surgery (SES, subretinal endoscopic surgery) for a man presenting with old SMH. The man was refusing, after years of treatment and administration of VEGF to the other eye, further administrations of VEGF. The standard approach was abandoned due to the lack of reliable data confirming the removal of old SMH by classical methods and the fact that such a procedure could be difficult to perform in this patient. The technology used in this example allows for very accurate and easy coagulation using endodiathermy during surgery, closing vessels that could lead to recurrent strokes or other pathologies. A distinguishing element of this procedure is also the ability of SES to remove subretinal polyps, which can be caused by vascular malformations in the course of the disease. Despite such capabilities of this procedure, it is not required to do a large retinotomy to achieve good results which drastically differentiates SES from PPV [31, 32].

An important part of the therapy is the administration of rtPA, which works by transforming plasminogen to plasmin and thus destroying the clot. Currently, mainly two types of therapy with this factor are performed – administration into the vitreous body and subretinal. The first way is simpler and less time-consuming, but the second brings rtPA closer to the target site of action. It appears that one way and the other achieves similar results in cases of SMH with etiology due to nAMD [33]. Recent techniques attempt to combine injections with rtPA and gas into other forms of therapy. Destruction of the clot in a mechanical manner can also be done using bubbles of gas injected into the clot along with rtPA. The gas forms a kind of clot-destroying foam and the administered compound has a larger surface area for action, this leads to faster removal of SMH. The use of air in this case speeds up the absorption of the gas (2 weeks as opposed to SF6 where it is 6 weeks) [34].

CONCLUSION

Although there are no official guidelines for SMH treatment, new clinical and case studies help us choose the most efficient treatment option. Some associations like American Academy of Ophthalmology propose complete algorithms of treatment in SMH. Depending on primary cause of SMH, patient–doctor cooperation possibilities and time from hemorrhage occurrence to treatment, we can propose different treatment options to our patients. A recent study review confirms that anti-VEGF therapy is a crucial part of AMD/PCV-related SMH management due to pathophysiology of these diseases. In case of small hemorrhages, anti-VEGF monotherapy, allows us to avoid surgery-related hazards. In post-traumatic or poor prognosis SMH surgical methods (pneumatic displacement, PPV) achieve better results. Pneumatic displacement, while efficacious in treating both recent and past traumatic injuries, comes with the downside of mandatory pronation post-op. Factors such as comorbidities and patient age may steer us towards less invasive methods. New, endoscopic treatment methods are noteworthy as they not only allow for thrombus removal, but also treating more complex intraocular pathologies while carrying less risk than standard PPV.

ADRES DO KORESPONDENCJI
med student Małgorzata Gawlak
Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University
30-705 Kraków, ul. Gustawa Herlinga-Grudzińskiego 1
e-mail: m@gawlak.pl

ORCID
Ada Pandey – ID – http://orcid.org/0000-0001-9467-1005
Alicja Chmura-Hołyst – ID – http://orcid.org/0000-0003-0733-1542
Dominika Prokop – ID – http://orcid.org/0000-0001-7318-7716
Oliwia Cwalina – ID – http://orcid.org/0000-0002-7071-0273
Ismael Alsoubie – ID – http://orcid.org/0000-00020974-3025
Bartosz Kuźlik – ID – http://orcid.org/0000-0001-8028-5525
Katarzyna Guzek – ID – http://orcid.org/0000-0003-1790-8667
Kinga Czarnacka – ID – http://orcid.org/0000-0002-6889-6507
Małgorzata Gawlak – ID – http://orcid.org/0000-0003-4573-1379
Maciej Kozak – ID – http://orcid.org/0000-0001-7993-2588
Ilona Pawlicka – ID – http://orcid.org/0000-0003-1556-7678
Katarzyna Sajak-Hydzik – ID – http://orcid.org/0000-0002-1973-2717
Agnieszka Piskorz – ID – http://orcid.org/0000-0003-4553-0497
Anna Roszkowska – ID – http://orcid.org/0000-0002-8083-3437

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