Submacular hemorrhage: treatment update and remaining challenges

Chee Wai Wong[1,2], Jan Carlo Yu Alegre[1], Yew San Ian Yeo[1,2], Chui Ming Gemmy Cheung[1,2]

[1]Singapore Eye Research Institute, Singapore National Eye Centre, Singapore; [2]Ophthalmology and Visual Sciences Academic Clinical Program, Duke-NUS Medical School, National University of Singapore, Singapore

Correspondence to: Dr. Chui Ming Gemmy Cheung. Singapore National Eye Centre, 11 Third Hospital Avenue, 168751, Singapore.
Email: gemmy.cheung.c.m@snec.com.sg.

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Abstract: Submacular haemorrhage (SMH) is a sight threatening complication that can occur in exudative age related macular degeneration (AMD), but has been described to occur more frequently in eyes with polypoidal choroidal vasculopathy (PCV). Left untreated, SMH carries a grave visual prognosis. Thus, expedient diagnosis and effective management of this complication is of paramount importance. The treatment strategies for SMH include (I) displacement of blood from the fovea, usually by injection of an expansile gas; (II) pharmacologic clot lysis such as with recombinant tissue plasminogen activator (rtPA); and (III) treatment of the underlying choroidal neovascularization (CNV) or PCV, such as with anti-vascular endothelial growth factor (anti-VEGF) agents. These three strategies have been employed in isolation or in combination, some concurrently and others in stages. rtPA has demonstrable effect on the liquefaction of submacular clots but there are remaining uncertainties with regards to the dose, safety and the timing of initial and repeat treatments. Potential side effects of rtPA include retinal pigment epithelial toxicity, increased risk of breakthrough vitreous haemorrhage and systemic toxicity. In cases presenting early, pneumatic displacement alone with anti-VEGF may be sufficient. Anti-VEGF monotherapy is a viable treatment option particularly in patients with thinner SMH and those who are unable to posture post pneumatic displacement.

Keywords: Submacular hemorrhage (SMH); recombinant tissue plasminogen activator (rtPA); polypoidal choroidal vasculopathy (PCV)

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Kitagawa *et al*., in their recent paper, addressed the difficult problem of submacular hemorrhage (SMH), a sight threatening complication seen in eyes with polypoidal choroidal vasculopathy (PCV). Their prospective study of 20 eyes found that with intravitreal injection of recombinant tissue plasminogen activator (rtPA), perfluoropropane (C_3F_8) and ranibizumab, complete displacement of SMH was achieved in 85% of eyes and 50% of eyes gained 3 lines or better visual acuity (VA) with no ocular or systemic adverse events, providing further evidence for the efficacy and safety of "non-vitrectomizing" techniques of SMH displacement (1).

Large SMH can occur in exudative age related macular degeneration (AMD), but has been described to occur more frequently in eyes with PCV. In 20% to 63.3% of cases, PCV has been found to be the cause of SMH (2-5). The incidence rate of massive SMH (defined as SMH greater than 4 disc diameters) in eyes with PCV was found to be 2.45% in the 1st year, increasing to 11.1% and 29.9% in 5 years and 10 years respectively. A cluster configuration of polyps conferred greater risk of SMH while combination treatment with PDT and anti VEGF reduced the risk of massive SMH developing (6).

It is important to distinguish between subretinal blood and sub-retinal pigment epithelial (RPE) blood as it is subretinal blood specifically that causes damage to the photoreceptors. Optical coherence tomography (OCT) is useful in distinguishing the level at which hemorrhage has occurred. Experimental data has shown that irreversible retinal damage can occur as early as 24 hours after onset of subretinal hemorrhage (7). The natural history of SMH confirms this fact: Left untreated, SMH carries a grave visual prognosis, with only 11% of eyes found to have best corrected visual acuity (BCVA) better than 20/200 after 2 years of observation in the submacular surgery trial (8). Hattenbach *et al*. emphasized the importance of early treatment in his study, which showed that eyes with SMH duration less than or equal to 14 days had the best visual outcome while none of the eyes with SMH duration >21 days showed any visual improvement (9). Thus, expedient diagnosis and effective management of this complication cannot be understated.

The treatment strategies for SMH 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. Published studies have employed these three strategies in isolation or in combination, some concurrently and others in stages. Several studies evaluating injection of rtPA combined with pneumatic displacement have reported VA gain of 3 lines or more in 42–66% (1,10,11). However, a number of issues require further clarification and will be discussed in this commentary. First, is intravitreal rtPA (non-vitrectomizing) as effective as subretinal rtPA (vitrectomizing) for lysis of clots; second, what is the ideal gas for pneumatic displacement; and third, is anti-vascular endothelial growth factor (anti-VEGF) treatment a viable monotherapy option?

Displacement of SMH away from the fovea with an expansile gas was first described by Heriot in 1996 (12), and is the mainstay for any technique that attempts to displace subretinal blood. The use of intravitreal rtPA with pneumatic displacement for the management of SMH was subsequently described by Hesse (13) and Hassan (14), who reported 45.5–67.7% of eyes achieving 2 or more lines improvement in VA. Since then, anti-VEGF had revolutionized treatment of neovascular AMD and its action could potentially be enhanced by the displacement of thick SMH from underlying CNV membranes or PCV (15).

Intravitreal injection of rtPA is less invasive and less technically challenging than vitrectomy with subretinal injection, and is thus a more attractive option for both the patient and the retinal physician. However, two important questions need to be addressed: First, can rtPA in the vitreous access the subretinal space? There is indirect evidence, both in animal and human studies, that rtPA injected into the vitreous can migrate across the retina and dissolve blood clots in the subretinal space. In rabbits, subretinal blood clots disappeared within 24 hours after intravitreal injection of rtPA (16). In patients with SMH secondary to exudative AMD, enlargement of subretinal hemorrhage in a gravity-dependent manner in 24 hours after intravitreous injection of rtPA has been observed (17). Second: is intravitreal injection of rtPA as effective as vitrectomy with subretinal injection of rtPA in dissolving and displacing subretinal blood clots? In a review of 38 studies, van Zeeburg *et al*. found no clear difference in complete displacement of SMH or complication rate between subretinal injection of rtPA with vitrectomy or intravitreal rtPA with pneumatic displacement (18). Recently, de Jong *et al*. conducted a small randomized controlled trial to compare the efficacy of vitrectomy and gas with subretinal rtPa *vs*. intravitreal rtPa with gas in displacing SMH. At 6 weeks postoperatively, he found a 100% reduction in subretinal blood volume in the subretinal injection group *vs*. 97% in the intravitreal group. This difference was not statistically significant. Fassbender *et al*. compared subretinal rtPA with intravitreal rtPA in a case control study and reported similar VA outcomes at 6 months, although final macular scar size was smaller in the subretinal rtPA group (19). Finally, Kitagawa's group demonstrated a complete displacement rate of 85% and partial displacement in 15% of eyes. These results suggest that rtPA injected via the intravitreal route may be sufficient to effect dissolution of SMH, and achieve similar efficacy as vitrectomy with subretinal rtPA without the associated risks of RPE rip and macular hole formation (20).

Safety concerns with rtPA should not be ignored. Photoreceptor loss and RPE damage have been described in animal studies (21,22). A recent study demonstrated increased degeneration of retinal ganglion cells in the presence of tissue plasminogen activator in a mouse model of glaucoma (23). Hesse *et al*. reported exudative retinal detachment followed by RPE hyperpigmentation in patients who received 100 µg of intravitreal rtPA (13). Kitagawa *et al*. noted no ocular or systemic adverse events with a rtPA dose of 20 µg/0.05 mL and suggested a safe dose of rtPA to be less than 25 µg/0.1 mL. Chen *et al*. reported a

case of widespread photoreceptor damage in the retinal periphery after 2 injections of rtPA 50 µg/0.1 mL, 3 days apart. The second injection was given in a gas filled eye. Repeat injections, especially with gas in the eye, could have concentrated rtPA at high doses near the retinal surface in the peripheral retina in patients who are posturing (24). Another important consideration is the risk of increased hemorrhage if rtPA is given within 72 hours of bleeding onset (25). Breakthrough vitreous hemorrhage can also occur and these complications will need to be thoroughly discussed with the patient during the informed consent process. Systemic side effects have not been reported, presumably because of the relatively low doses given and small sample sizes not powered to study these side effects, but hemorrhagic complications should not be forgotten in susceptible patients, such as those on anti-coagulants.

In light of these concerns and the high cost of rtPA, a more "moderate" approach of pneumatic displacement alone with anti-VEGF injection may also be considered, particularly in patients presenting with early SMH. Ohji *et al*. demonstrated an 80% complete displacement rate in eyes with SMH treated with pneumatic displacement within 6 days of onset (26). In the review by Stanescu-Segall *et al*. of 110 cases of SMH, a displacement rate of 65% was reported (27). Shin *et al*. showed similar efficacy of pneumatic displacement with anti-VEGF as compared to anti-VEGF monotherapy in terms of BCVA at 6 months, with the added benefit of faster visual recovery (4). In contrast, Fassbender *et al*. found no significant improvement in VA or macular scar area following pneumatic displacement without rtPA.

The optimal choice of gas for pneumatic displacement is unclear. The ideal gas for pneumatic displacement should effectively displace SMH while minimizing duration inside the eye. SF_6 has the advantage of faster dissolution, earlier recovery of vision and lower risk of cataract progression. while C_3F_8 continues to expand over the next 3–4 days and therefore necessitates more frequent monitoring of intraocular pressure (IOP) (28). Olivier *et al*. achieved 86% total displacement of SMH using air alone, following vitrectomy and subretinal rtPA injection (15). In non vitrectomized eyes however, an expansile gas is needed to achieve sufficient gas fill for pneumatic displacement. In a study of eyes with SMH treated with pneumatic displacement alone, Ron *et al*. found a significantly greater proportion of eyes with 2 snellen lines improvement in the the SF_6 group (54%) compared to the C_3F_8 group. The reasons for this difference was not apparent from the study (29).

As previously discussed, the use of anti-VEGF is an important component of management, but is anti-VEGF monotherapy a viable therapeutic strategy for SMH? Studies evaluating anti-VEGF monotherapy with either bevacizumab, ranibizumab or aflibercept have shown an improvement in VA of 3 lines or more in 44–60% at 6 months, comparable to results achieved with rtPA (5,30-33). 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 (4). Better visual outcome was achieved with combination therapy at 6 months in the subgroup of eyes with SMH thicker than 450 µm, while no difference was seen for SMH less than 450 µm. These results suggest that combination therapy may be more useful for patients who require faster visual improvement and in patients with thicker SMH. In summary, anti-VEGF monotherapy is a viable option, but the choice of anti-VEGF and whether anti-VEGF monotherapy can replace combination therapy will need to be examined in future randomized controlled trials.

In conclusion, SMH is a challenging situation and multiple therapeutic approaches have been put forward with variable success. The evidence for the optimal treatment is limited. However, based on current available literature, a non-vitrectomizing approach of intravitreal rtPA, pneumatic displacement and intravitreal anti-VEGF is a reasonable option. rtPA has demonstrable effect on the liquefaction of submacular clots but there are remaining uncertainties with regards to the dose, safety and the timing of initial and repeat treatments. In cases presenting early, pneumatic displacement alone with anti-VEGF may be sufficient. There appears to be no added advantage of using a longer acting gas for pneumatic displacement. Anti-VEGF monotherapy should be applied with caution as delayed resolution of subfoveal blood may potentially cause further damage to photoreceptors from prolonged exposure to SMH, although current studies have shown comparable final visual outcome with combination therapy. However, it remains a viable treatment option in patients with thinner SMH and those who are unable to posture.

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Footnote

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