Editorial

Management of subretinal hemorrhage

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Provenance: This is a Guest Editorial commissioned by Section Editor Yi Sun, MD (Department of Ophthalmology, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China).

Comment on: Kitagawa Y, Shimada H, Mori R, *et al*. Intravitreal Tissue Plasminogen Activator, Ranibizumab, and Gas Injection for Submacular Hemorrhage in Polypoidal Choroidal Vasculopathy. Ophthalmology 2016;123:1278-86.

Abstract: Subretinal hemorrhage is a vision threatening complication of exudative age related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV). Timely removal or displacement of subretinal hemorrhage from the central macula, ideally within 7 to 10 days after onset, is critical to allowing potential recovery of vision. Surgical techniques with the use of a bubble to displace the subretinal hemorrhage can now be performed with tissue plasminogen activator to lyze the blood and with or without vitrectomy.

Keywords: Subretinal hemorrhage; age related macular degeneration (AMD); polypoidal choroidal vasculopathy (PCV); vitrectomy; tissue plasminogen activator; intraocular gas bubble

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Subretinal hemorrhage is a vision threatening complication of exudative age related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV) (1,2). PCV is a subtype of type I subretinal neovascularization and of wet macular degeneration (3). The visual prognosis following subretinal hemorrhage depends on whether or not it involves the fovea, the duration of the subretinal hemorrhage, and the thickness of the subretinal hemorrhage under the fovea (4). If the hemorrhage does involve the fovea, and is thickly elevating the fovea (4), and it has been present for a relatively short duration before retinal damage has occurred (in general one to two weeks or less), then surgical intervention may be helpful by removing or displacing the subretinal hemorrhage out from under the fovea.

The damage to the photoreceptors occurs due to the toxicity of the blood under the retina, due to prevention of nutrient flow from the choriocapillaris to the photoreceptors, and due to fibrin interdigitating within the photoreceptor outer segments (5). Because of this, tissue plasminogen activator (t-pa) has been utilized to lyze the fibrin and to liquefy the subretinal blood. The subretinal blood can be removed after placement of subretinal t-pa under the retina through a subretinal injection during vitrectomy, and then evacuating the blood, as previously described in 2001 by Haupert and colleagues (6). Another option during vitrectomy is to not remove the subretinal hemorrhage after placement of t-pa, but to displace the subretinal hemorrhage from the fovea after placement of the subretinal t-pa by using a partial air or gas fill and proper patient positioning. Initial sitting up positioning to displace the subretinal hemorrhage after fibrinolysis followed by face down positioning to further displace hemorrhage from the macula is often utilized. This is usually accomplished by a partial air or gas fill in the vitreous, which can then displace the subretinal hemorrhage from the fovea. In a recent paper by Kimura and colleagues (7) utilizing vitrectomy with subretinal injection of 4,000 IU of subretinal t-pa in 15 consecutive cases, the subretinal hemorrhage was successfully displaced

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from the fovea in all cases intraoperatively. Vision improved significantly with 80% of eyes recovering 20/40 or better vision, and all eyes receiving ranibizumab or aflibercept as postoperative therapy to control exudative changes on an as needed basis. The authors stressed the importance of timely removal of subretinal hemorrhage based on their results, ideally within 7 to 10 days after onset. Another surgical option during vitrectomy is to place a subretinal air bubble after placement of the subretinal t-pa, which the authors felt more immediately displaced subretinal hemorrhage from the fovea after lysis of the subretinal hemorrhage by the subretinal t-pa (8). This subretinal air quickly displaced the subretinal hemorrhage from the fovea, which was accomplished in 100% of cases intraoperatively.

In a recent paper in *Ophthalmology*, Kitagawa and colleagues (9) presented the use of a procedure to displace blood without the need for a vitrectomy. They utilized multiple injections into the vitreous cavity with intravitreal t-pa, an intravitreal antiangiogenic medication, and a long acting gas bubble. A paracentesis was performed preinjection to allow placement of the volume of the multiple intravitreal injections. Three sequential injections were then given using t-pa (25 μg/0.05 mL), 100% perfluoropropane gas (0.3 mL), and ranibizumab (0.5 mL/0.05 mL) (7). Patients initially were instructed to sit up for 2 hours and then positioned face down for 2 days. The authors reported displacement of the subretinal hemorrhage from the fovea at one week after treatment in 85% of cases (17/20 eyes) and partial displacement in 15% (3/20 eyes). Postoperative visual acuity improved significantly and 60% of eyes recovered 20/40 or better vision with all of these eyes with good vision recovery having complete displacement of subretinal hemorrhage from the fovea by one week after the procedure.

Based on animal studies, the use of t-pa as an intravitreal injection for subretinal hemorrhage has been controversial. Intravitreal fluorescein isothiocyanate-labelled t-pa did not diffuse into or across the retina in a rabbit model by Kamei *et al*. (10). This would makes it less likely to be effective as an intravitreal injection. However, the internal limiting membrane (ILM) is thinner in the fovea of the human eye than the rabbit eye, and there could be alterations in the ILM after an acute subretinal hemorrhage that allows the t-pa to penetrate. In a different animal model study, Coll *et al*. demonstrated that intravitreally injected tPA (50 μg) routinely induced complete lysis of 1-day-old subretinal blood clots under intact retina in an albino rabbit model (11). In a retrospective clinical study of management the use of intravitreal t-pa and subretinal t-pa were compared as to the effectiveness of displacement of subretinal hemorrhage. During vitrectomy 40 μg of t-pa was injected intravitreally in one group and 10 to 20 μg of t-pa was injected subretinally in the other group. There was a significantly higher rate of complete displacement of subretinal hemorrhage in the subretinal t-pa group than in the intravitreal injection of t-pa group (12).

When subretinal hemorrhage involves the central fovea, is thickly elevating the fovea, and has occurred relatively recently within one to two weeks, then surgical intervention has a good chance of visual improvement better than the natural history of thick submacular hemorrhage, which usually results in poor vision. There are now useful techniques to surgically displace the subretinal hemorrhage with and without vitrectomy. The most immediate displacement of subretinal hemorrhage can be accomplished with the use of subretinal t-pa during vitrectomy with surgeons reporting successful displacement of subretinal hemorrhage very quickly (7). New innovations such as the use of subretinal air after lysis of the subretinal hemorrhage with t-pa can potentially result in almost immediate displacement of subretinal hemorrhage intraoperatively (8). However, there are intraoperative risks of vitrectomy and subretinal surgery, and in some clinical situations there may not be an immediate access to an operating facility with vitrectomy and subretinal t-pa. In the paper by Kitagawa and associates (9), excellent improvement can now sometimes be obtained with a procedure not involving vitrectomy, and avoiding the risks of vitrectomy and subretinal injection. This procedure of sequential intravitreal injections of t-pa, intraocular long acting gas, and antiangiogenic medication can allow displacement of subretinal hemorrhage with significant improvement in visual results from the natural history of thick subretinal hemorrhage. Following displacement of subretinal hemorrhage all recent papers have emphasized careful clinical follow-up and continued management of active leaking with antiangiogenic therapy for the exudative age-related macular degeneration or polypoidal chroroidal vascuopathy.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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