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Case Report

Non-vitrectomizing vitreous surgery and adjuvant intravitreal tissue plasminogen activator for non-recent massive premacular hemorrhage

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Abstract

Massive premacular hemorrhage can cause sudden visual loss. We sought to evaluate the efficacy, safety and visual outcome of non-vitrectomizing vitreous surgery with intravitreal tissue plasminogen activator (t-pa) for long-lasting thick premacular hemorrhage. This retrospective, interventional study examined three consecutive eyes of three patients who received nonvitrectomizing vitreous surgery with intravitreal t-pa for the treatment of non-recent massive premacular hemorrhage. Detailed ophthalmoscopic examinations were performed pre- and postoperatively to evaluate the visual outcome, the resolution of premacular hemorrhage and the changes in lenticular opacity.In all three eyes, the premacular hemorrhage cleared after the procedure. Final best-corrected visual acuities improved from 6/30 to 6/10 in patient 1, 2/60 to 6/4 in patient 2, and 3/60 to 6/6 in patient 3. Operated and fellow eyes did not differ in terms of nuclear sclerosis. No complications from the procedure were noted.In these selected cases, nonvitrectomizing vitreous surgery with intravitreal t-pa was an effective and safe alternative treatment for non-recent massive premacular hemorrhage.

Keywords: intravitreal injection; nonvitrectomizing vitreous surgery; premacular hemorrhage; tissue plasminogen activator; vitrectomy

1. Introduction

Premacular hemorrhage, or hemorrhage into the subhyaloid or sub-internal limiting membrane (sub-ILM) space at the macular area, can cause sudden visual loss. It results from a variety of diseases, including diabetic retinopathy, retinal arterial macroaneurysm, Valsalva maculopathy, hematologic disorders, trauma and surgical complications.[1,2] Patients with premacular hemorrhage can be managed with observation, while vitrectomy is also an option for nonclearing hemorrhage. However, the hemorrhage may take a long time to clear spontaneously, and it may result in late macular traction and permanent macular damage.[1] Vitrectomy may result in post-vitrectomy nuclear sclerosis.[3]

In recent years, several alternative treatments have been proposed to accelerate blood clearance, such as membranotomy with different laser modalities, intravitreal injection of tissue plasminogen activator (t-pa) and pneumatic displacement.[2,4–6] Outcomes vary by approach. Laser membranotomy, which creates an opening to drain the hemorrhage, is reported effective in patients with premacular hemorrhage of no longer than 21 days' duration; however, it may have limited effects and take longer to drain in patients with hemorrhages of more than two weeks' duration.[7]

In 1999, Saito et al.[8] advocated nonvitrectomizing vitreous surgery for macular pucker to prevent postoperative nuclear sclerosis; the procedure consisted of epi-retinal membrane peeling without cutting or removing the vitreous. We applied this concept to manage premacular hemorrhage, and a bent needle was used to create a membranotomy to immediately drain the blood into the vitreous cavity. The results were favorable in patients with recent premacular hemorrhage;[9] however, we observed slow or no drainage through the

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opening in patients with non-recent hemorrhage longer than 2 weeks. Consequently, we added adjuvant intravitreal t-pa to promote blood drainage in sustained hemorrhage lasting longer than two weeks. In this retrospective series, we evaluated the resolution of hemorrhage, visual outcome and changes in lenticular opacity after surgery.

2. Case report

The study was approved by the hospital institutional review board (IRB) committee. Three eyes of three consecutive patients with thick premacular hemorrhage secondary to different causes were enrolled in this study between November 2007 and August 2008 (Table 1). Only massive, subhyaloid or subinternal limiting membrane (sub-ILM) hemorrhage blocking the view of the fovea was considered for treatment. Premacular hemorrhages along with other complicated situations were all excluded, including retinal detachment, vitreous hemorrhage, proliferative vitreoretinopathy, proliferative diabetic retinopathy and significant cataracts that interfered with intraoperative visibility.

Details from preoperative ophthalmological examinations were recorded, including visual acuity, intraocular pressure, slit lamp biomicroscopy, indirect ophthalmoscopy and fundus photographs after dilation of the pupils with 10% phenylephrine and 1% tropicamide. After the procedure was explained, informed consent was obtained from all patients, and all surgical procedures were performed by the same surgeon (TT Wu).

We performed the procedure with the patient in the supine position under local anesthesia. After prepping the eye with 5% betadine, nonvitrectomizing vitreous surgery was done using transconjunctival sutureless 25-gauge vitrectomy technique without creating an infusion port. The trocar puncture and cannula insertion were made at the pars plana, only in the superotemporal and superonasal quadrants. Through the cannula, a fiberoptic light source and a bent 25-gauge needle filled with 50 μg/0.1 ml t-pa were introduced while using a hand-held vitrectomy lens. Without cutting the vitreous or performing any other intraocular maneuver, we used the bent needle to perform the membranotomy directly. The created opening on the anterior surface of the membrane provided an access for subhyaloid or sub-ILM hemorrhage to enter the vitreous cavity. At the conclusion of the procedure, we injected 50 μg/0.1 ml t-pa through the needle. After the cannulas and their plugs were withdrawn one after the other, the scleral wounds sealed without wound leaks. All patients were examined at 1 day, 1 week, 3 weeks, 5 weeks, and 3 months postoperatively, and then every 3 months thereafter. Slit lamp examination and indirect ophthalmoscopy were performed at every visit. The efficacy and outcome of the procedure were assessed by the drainage and clearing of the premacular hemorrhage, visual improvement and changes in lenticular opacity.

The recorded data for all patients included the following: gender, age, lens status, cause and duration of hemorrhage, fundus photographs, preoperative best-corrected visual acuity and postoperative best-corrected visual acuity at each follow-up time point. We graded lens opacity using the scale reported previously by Thompson et al.[3] : 0, clear lens; 0.50, trace cataract; 0.75, minimal cataract; 1.00, mild (judged to have no effect on visual acuity); 2.00, moderate (decreasing visual acuity, but good view of retina by contact lens biomicroscopy); 3.00, moderately severe (impaired visual acuity and some distortion or impaired view of retina); and 4.00, severe (very poor view of retina).

Table 1 provides a summary of the collected data. Of the three patients, one was a 27-year-old female and two were 52-year-old males. All three eyes were phakic. Causes of premacular hemorrhage were retinal arterial macroaneurysm, head injury and ocular trauma. The time to surgery ranged from 15 to 35 days. Preoperative visual acuities ranged from 2/60 to 6/30. After nonvitrectomizing vitreous surgery with intravitreal t-pa, final vision improved to 6/10, 6/4, and 6/6.

Patient 1 was a 52-year-old male with a history of poorly controlled hypertension who was evaluated because of blurred vision in his left eye for more than one month. His best-corrected visual acuity was 6/6 in the right eye and 6/30 in the left eye, and grade of nuclear sclerosis was 0.5 in both eyes. Dilated fundus examination revealed retinal arterial macroaneurysm with premacular hemorrhage of 11 disc areas in the left eye (Fig. 1A). Faint vitreous hemorrhage was noticed soon after the operation (Fig. 1B), and the sclerotomy wound sealed well without signs of hypotony or endophthalmitis. Vision recovered to 6/10 in the left eye, and the residual vitreous hemorrhage disappeared completely in two months (Fig. 1C). Both vision and lens status remained stable during three years of follow-up.

Table 1
Clinical characteristics of patients with non-recent premacular hemorrhage before and after non-vitrectomizing vitreous surgery and intravitreal t-pa.

Patient	Sex/Age (years)	Eye	Cause	Duration of symptoms (days)	Size (DD)	BCVA		Grade of nuclear sclerosis*		Vitreous clear-up time (months)	Follow-up (months)
						Initial	Final	Initial	Final		
1	M/52	L	RAM	35	11	6/30	6/10	0.5	0.5	2	36
2	F/27	R	Terson syndrome	30	10	2/60	6/4	0	0	2	24
3	M/52	L	Ocular injury	15	9	3/60	6/6	0.75	0.75	2	30

F, female; M, male; R, right eye; L, left eye; RAM, retinal arterial macroaneurysm; DD, disc diameter; BCVA, best-corrected visual acuity.
* Degree of nuclear sclerosis was graded according to the scale reported by Thompson et al.[3] at initial and final examinations: 0, clear lens; 0.50, trace cataract; 0.75, minimal cataract.

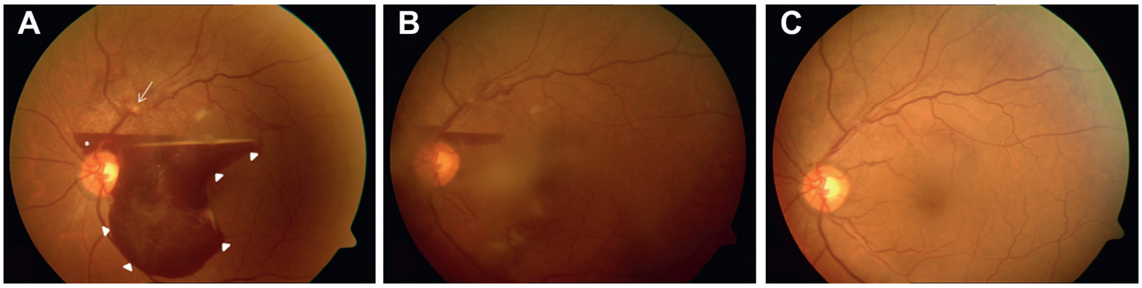

Fig. 1. Patient 1. A. Retinal arterial macroaneurysm (arrow) with premacular hemorrhage of 11 disc areas in size in the left eye. There were two levels of blood accumulation: subhyaloid (delineated by arrowheads) and subinternal limiting membrane (asterisk) hemorrhage (visual acuity = 6/30). B. On the day after 25-gauge nonvitrectomizing vitreous surgery and intravitreal injection of t-pa, the premacular hemorrhage was drained, with faint vitreous hemorrhage and residual subinternal limiting membrane hemorrhage superior to the optic disc. C. The residual blood cleared gradually within two months (visual acuity = 6/10).

Patient 2 was a 27-year-old female who survived a traffic accident with the sequelae of subdural and epidural hematoma. This patient was referred due to blurred vision in the right eye for more than one month. She had clear lens in both eyes, and best-corrected vision was 2/60 in the right eye and 6/5 in the left eye. Fundus examination revealed premacular hemorrhage of 10 disc areas in the right eye and papilloedema in both eyes (Fig. 2A). Nonvitrectomizing vitreous surgery with 25-gauge sutureless equipment was carried out with posterior hyaloid membrane peeling and intravitreal injection of t-pa. Faint vitreous hemorrhage was noted after the operation (Fig. 2B). Six weeks later, the vision returned to 6/4 in the right eye with residual vitreous opacity inferiorly (Fig. 2C). Vision was stable, and the lens remained crystal clear two years after the operation.

Patient 3 was a 52-year-old male with blurred vision in the left eye for 15 days due to trauma. Best-corrected vision was 6/6 in the right eye and 3/60 in the left eye, and degree of nuclear sclerosis was 0.75 in both eyes. Intraocular pressure and anterior segment were normal. Indirect ophthalmoscopy revealed premacular hemorrhage of 9 disc areas in the left eye (Fig. 3A). After this procedure, faint vitreous hemorrhage was noted, but it was absorbed completely within two months, with visual recovery to 6/6 in the left eye (Fig. 3B). Lens status and vision remained stable after 30 months.

The surgery was accomplished without complications in all three eyes. In all cases, most of the premacular hemorrhage drained into the vitreous cavity on the first postoperative day. The vitreous hemorrhage would gravitate to the lower part of the vitreous cavity; as a result, all patients experienced visual improvement on the day after surgery. Neither postoperative hypotony nor infection was noticed during follow-up. For all, vitreous hemorrhage cleared completely within two months.

All patients were followed up for at least 2 years (range, 24-36 months), and all three eyes had at least 4 lines of Snellen visual acuity improvement at final follow-up. There were no late complications, including retinal tear, retinal detachment or endophthalmitis, during follow-up. All three patients had equal degree of nuclear sclerosis in both eyes before the operation, and they remained unchanged after the operation. At final examination, all three phakic eyes and the fellow eyes were no different in terms of degree and progression of nuclear sclerosis (Table 1).

3. Discussion

Premacular hemorrhage can cause sudden visual loss. The hemorrhage may occur in a space created by a posterior vitreous detachment (subhyaloid or retrohyaloid hemorrhage) or between the internal limiting membrane and the retinal nerve fiber layer (sub-ILM hemorrhage), but the definite location of the premacular hemorrhage may be difficult to distinguish clinically. Reported causes of premacular hemorrhage have included ocular injury, Terson syndrome, shaken baby syndrome, retinal arterial macroaneurysm, valsava maculopathy, diabetic retinopathy, branch retinal vein occlusion, surgical complications, anemia and various hematological disorders.[1,2] Several options are feasible to manage this

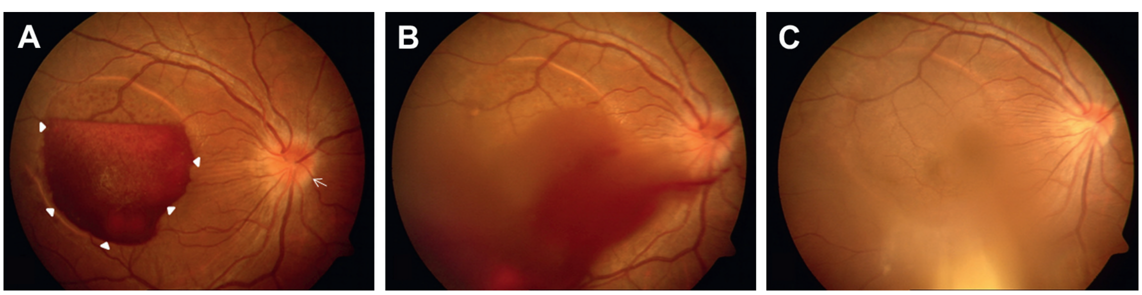

Fig. 2. Patient 2. A. Premacular hemorrhage (delineated by arrowheads) of 10 disc areas in size and papilloedema (arrow) in the right eye (visual acuity = 2/60). B. On the day after the operation, faint vitreous hemorrhage was noted. C. Six weeks later, residual vitreous opacity had gravitated inferiorly in the right eye (visual acuity = 6/4).

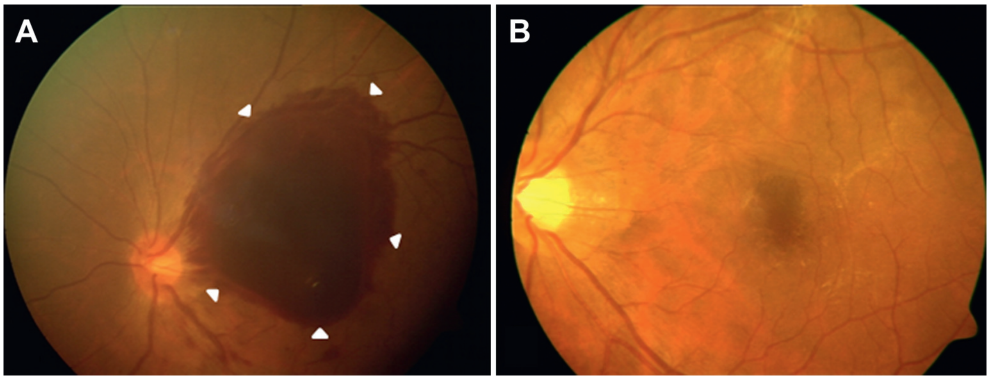

Fig. 3. Patient 3. A. Fundus revealed premacular hemorrhage (delineated by arrowheads) of 9 disc areas in the left eye. B. After non-vitrectomizing vitreous surgery, the residual hemorrhage was resorbed gradually.

condition. One may allow the hemorrhage to clear spontaneously, but this process can take several months. The toxic effects of iron released from the hemoglobin may cause irreversible damage to the retina and many intraocular structures; in addition, formation of an epiretinal membrane with late macular traction in some cases may result in poor visual prognosis.[1] Vitrectomy is a well established method for managing nonclearing premacular hemorrhage, and it can remove the hemorrhage immediately to restore vision while allowing anatomical definition of the exact location of the hemorrhage and histological analysis of the removed anterior wall of the hemorrhage. However, complications include bleeding, retinal breaks, retinal detachment, macular injury, proliferative vitreoretinopathy, accidental lens damage and nuclear sclerosis.[3,10] Although the incidence of post-vitrectomy nuclear sclerotic cataract is relatively low in patients younger than 50 years old, it increases over time, as observed during long-term follow-up.[10] Subsequently, a second surgery is usually required for cataract extraction.

Laser photodisruption of the surface membrane entrapping the hemorrhage has been reported using several different types of lasers: pulsed Q-switching Nd:YAG, frequency-doubled Nd:YAG, argon and krypton laser.[2,4,5,11] Laser membranotomy creates an exit for the blood into the vitreous cavity, leading to prompt visual improvement and facilitating blood resorption. However, accidental retinal injury by laser may occur,[12] caused by direct or reflected beams of the laser. Complications of the laser modality are subretinal, retinal, choroidal and vitreous hemorrhage; retinal hole; and subsequent macular pucker and macular hole formation.[12] The probability of retinal and choroidal injury is increased when the fundamental mode beam is focused less than 4 mm from the retinal surface.[12] Furthermore, several pulses are usually attempted before creating a patent membranotomy, and the built-up laser energy might somehow injure the intraocular tissues.

Saito et al. reported using nonvitrectomizing vitreous surgery for macular pucker to prevent postoperative nuclear sclerotic cataracts.[8] We applied this technique to treat premacular hemorrhage.[9] As in laser membranotomy, the opening created at the most dependent part of the anterior surface of the hemorrhage allows the blood to enter the vitreous cavity, permitting immediate drainage. The opening can be easily sized to optimize drainage, releasing the trapped blood from the subhyaloid or sub-ILM area. The hemorrhage obstructing the macular area sinks to the lower part of the vitreous, leading to prompt improvement in visual function with resolution of the hemorrhage.

Consequently, nonvitrectomizing vitreous surgery may save time, compared with standard vitrectomy.[9] Use of 25-gauge sutureless equipment may make the procedure much easier and faster, and speed wound healing, as in our patients.

It has been noted that Nd:YAG laser membranotomy was effective in cases of premacular hemorrhages of less than three weeks' duration; however, in cases with more than two weeks' duration, drainage of the hemorrhage was slower, with little change immediately after the treatment.[7] In our patients with relatively longer duration of premacular hemorrhage, we observed slow or no drainage after creating a membranotomy. Subsequently, we injected t-pa intravitreally to accelerate lysis of blood clots, improve the rate of clearance, and promote a good surgical outcome.

Intraocular injection of t-pa has been administered as an adjuvant therapy for eye diseases for many years. T-pa is a fibrinolytic agent which can dissolve fibrin clots rapidly and is widely used for lysis of intraocular fibrin, hyphema, submacular hemorrhage, premacular hemorrhage, postvitrectomy fibrin formation and occluded peripheral iridectomy.[6,13] Besides inducing clot liquefaction, t-pa may also enhance separation of the vitreous, loosening the vitreoretinal adherence that confines the premacular hemorrhage;[6] therefore, the resultant mobile blood may be drained more easily.

The dosage at which t-pa causes retinal toxicity is not clear, but some studies found no toxic reactions after intraocular injection of up to 50 μg.[14,15] T-pa may raise the risk of rebleeding, hyphema and vitreous hemorrhage. In our cases, it did not produce serious adverse effects. As in patients without t-pa in a previous report,[9] the resulting vitreous hemorrhage was so mild that it did not obscure or impede the visual axis significantly. Vision improved soon after drainage of dense hemorrhage from the premacular area.

In all three patients, the resorption of residual vitreous hemorrhage took about 2 months. No complications, including hypotony, retinal detachment or endophthalmitis, was noted, and the lens status remained stable and comparable to the fellow eye at last follow-up visit (range, 24-36 months).

The extent of visual improvement and prognosis accorded with the underlying causes and preexisting macular diseases. In our study, final vision recovered to a level above or equal to 6/6 in patients without significant macular pathology (patients 2 and 3), while the final vision of patient 1 was less desirable. This result was probably due to some underlying macular pathology and concurrent subretinal hemorrhage from retinal arterial macroaneurysm in the patient. Raymond[4] also found poor visual outcome after Nd:YAG laser treatment in one case because of persistent, pre-existing subretinal hemorrhage from a macroaneurysm. Moreover, eyes with premacular hemorrhage secondary to macroaneurysm or diabetic retinopathy may need longer to recover.[5]

In this study, we achieved good outcomes of non-vitrectomizing vitreous surgery and intravitreal t-pa injection in three patients with non-recent premacular hemorrhage. An injection of intravitreal t-pa may help manage longstanding premacular hemorrhage. There was neither complication nor detectable progression of nuclear sclerosis during follow-up. We conclude this procedure may be a safe and effective alternative treatment for selected patients with non-recent premacular hemorrhage. It shows promise in eliminating the need for standard vitrectomy and preventing postoperative nuclear sclerosis. However, due to strict candidate selection, we had limited case number and lacked a control group. Further large-scale and long-term studies, preferably in a prospective, randomized design of all available treatment modalities, are necessary to define the benefits and disadvantages of this procedure.

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