EXTENDED REPORT

Pars plana vitrectomy with peripheral retinotomy after injection of preoperative intravitreal tissue plasminogen activator: a modified procedure to drain massive subretinal haemorrhage

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Aims: To report outcome of a modified procedure for draining massive subretinal haemorrhages (SRHs).

Methods: The charts of eight consecutive eyes from eight patients with massive SRHs extending to the periphery and involving two or more quadrants with haemorrhagic and bullous retinal detachment were reviewed. Tissue plasminogen activator (tPA) was injected intravitreally 12–24 h preoperatively; vitrectomy was carried out with peripheral retinotomy, drainage of the SRH from the retinotomy using perfluorocarbon liquid and gas tamponade with prone positioning postoperatively.

Results: The preoperative visual acuities ranged from light perception to 20/200. Most of the subretinal haematomas moved postoperatively to the vitreous cavity through the peripheral retinotomy using perfluorocarbon liquid. Residual SRHs were drained from the anterior chamber at the bedside after prone positioning overnight. SRH recurred in one eye 14 months postoperatively and was successfully retreated. No other serious complications developed. The final visual acuity improved in seven eyes (range 20/1000–20/60). Polypoidal lesions in choroidal vasculatures were present in three of seven patients.

Conclusions: The technique seems safe and effective for treating massive SRH. However, visual recovery is limited by the underlying macular pathology. Polypoidal choroidal vasculopathy, other than age-related macular degeneration, may be another cause of massive SRHs.

Large, thick subretinal hemorrhages (SRHs) caused by age-related macular degeneration often result in a poor visual outcome, especially when the haemorrhage is massive and extends to the periphery. In this case, the central visual acuity and the visual fields are seriously affected.^{1–5}

Recent advances in vitreoretinal surgical techniques over the past decade facilitate removal of SRHs from the subretinal space in the macular area.^{6–10} Vitrectomy with subretinal injection of tissue plasminogen activator (tPA) and use of perfluorocarbon liquid to safely evacuate the liquefied clot from the submacular space have improved the surgical outcome.^{7–10} Pneumatic displacement of SRHs from the macula by intravitreal injection of expansile gas with tPA¹¹ or without tPA is also a useful technique to improve vision and is now the first treatment of choice in most new patients.^{12–15} However, when an SRH is massive and extends peripherally to form large haemorrhagic retinal detachments, it is difficult to displace or evacuate the subretinal clots using the previously described techniques.¹² To evacuate massive SRHs related to AMD, creation of large peripheral retinotomies ranging from 180° to 360° with or without macular translocations have been reported.^{16–18} However, creation of a large retinotomy can be followed by development of postoperative complications. Visual outcome is disappointing despite these surgical interventions.

To minimise surgically induced complications, we performed a newly modified surgical procedure consisting of intravitreal injection of tPA before operation and subsequent vitrectomy to force the SRH through the peripheral small retinotomy using perfluorocarbon liquid and long-acting gas. The purpose of this study was to investigate the efficacy and safety of treating massive SRHs with this less invasive surgical procedure.

MATERIALS AND METHODS

We retrospectively reviewed a consecutive series of eight eyes of eight patients who underwent preoperative intravitreal injection of tPA followed by a planned vitrectomy to remove a massive SRH. All patients were treated at the Department of Ophthalmology, Osaka University Hospital (Osaka, Japan) from April 2002 to March 2005. A massive SRH was defined as extending to the periphery more than two quadrants to form haemorrhagic and bullous retinal detachments. In patients in whom the fundus was obscured by vitreous haemorrhage, the extent of the SRH was measured by B-scan echography. After the institutional review board committee of Osaka University Hospital approved the treatment, written informed consent was obtained from all patients after they received a detailed description of the procedure.

After topical anaesthesia was induced with 4% lidocaine eye drops and the conjunctiva was disinfected with povidone-iodine solution, 25 µg of recombinant tPA (Activacin, Kyowa Hokko Kogyo, Tokyo, Japan) in 0.1 ml balanced saline solution was injected intravitreally with a 30-gauge needle at the bedside about 12–24 h before the vitrectomy to liquefy the subretinal clot. Clot liquefaction was confirmed by changes in configuration of the haemorrhagic retinal detachment, with eye movement during fundus examination, echographic examination or both. Pars plana vitrectomy was then performed. Phacoemulsification and aspiration were performed simultaneously in the eyes with a cataract. After extensive removal of vitreous gel at the vitreous base, one or two peripheral

Abbreviations: AMD, age-related macular degeneration; logMAR, logarithm of minimal angle of resolution; SRH, subretinal haemorrhage; tPA, tissue plasminogen activator

retinotomies within approximately 15° of each other were created superotemporally, inferotemporally or both. Perfluorocarbon liquid (Perfluoron, Alcon Laboratories, Fort Worth, Texas, USA) was dropped on the posterior retina to form a single bubble; the enlarging bubble displaced the liquefied subretinal blood from the posterior pole to the periphery (fig 1). The liquefied subretinal blood was then forced into the vitreous cavity through the peripheral retinotomy by gently rocking the eyeball. The haemorrhage in the vitreous cavity was aspirated; this manoeuvre was repeated until most of the liquefied subretinal blood, which was recognised by its movement beneath the detached retina, was displaced from the subretinal spaces. After cryoretinopexy was applied around the retinotomies, fluid–air exchange with complete removal of the perfluorocarbon liquid was performed and a non-expansile concentration of 14% perfluoropropane was infused. The patient was instructed to remain in a prone position postoperatively for at least 24 h to force out the residual subretinal blood through the peripheral retinotomies. If the residual blood was successfully forced into the vitreous cavity and accumulated in the anterior chamber after the patient remained prone overnight, the blood was drained at the bedside with a 27-gauge needle through the corneal limbus by a fluid–air exchange technique.

Medical records of the patients were reviewed for age, sex, follow-up period, preoperative best-corrected visual acuity, best postoperative visual acuity and final visual acuity defined as the best-corrected visual acuity at the most recent follow-up visit, surgical complications, duration and recurrence of SRH, and the time from surgery to recurrence. Fluorescein and indocyanine green angiographic images, if available, were reviewed to identify the cause of the massive SRH. Visual acuity was measured using the Landolt C acuity chart and analysed on a logarithm of minimal angle of resolution (logMAR) scale. For analysis, counting fingers vision was converted to 20/8000

(doubling of the visual angle of 1/200), hand motions to 20/16 000 and light perception to 20/32 000. $p < 0.05$ indicated significance.

RESULTS

Table 1 summarises the patient data. Seven men and one woman were included in this study (mean age 70.8 years; range 52–91 years). The mean duration of SRH before treatment was 10 days (range 2–21 days). The mean follow-up period was 23 months (range 12–36 months).

Vitreous haemorrhage was complicated in 3 (38%) of the eight eyes at the initial examination. Haemorrhagic and bullous retinal detachment extended to two quadrants (fig 1) in one eye, three quadrants (fig 2) in three eyes and four quadrants (fig 3) in four eyes. Before surgery, pneumatic displacement of SRH with intravitreal tPA was attempted in the initial two eyes, but failed. Intraoperative examination showed that the macula was involved in the SRH lesions in all study eyes.

Most of the SRHs were successfully evacuated from the subretinal spaces, and the raised retina was flattened in all eight eyes; substantially thinner blood was beneath the peripheral retina at the end of surgery. Although 4 of 8 (50%) eyes still required drainage of the residual blood from the anterior chamber at the bedside on the first postoperative day, no further surgery was required to remove the residual SRH. The blood that accumulated in the anterior chamber was considered to be the liquefied subretinal blood that was forced into the vitreous cavity through the retinotomies as the result of overnight prone positioning and gas tamponade. One month after surgery, most of the residual SRH was absorbed and the retina was presumably well reattached, with minimal retinal pigment epithelium damage in the areas of the previous haemorrhagic retinal detachments. Fluorescein and indocyanine green angiographic images from seven eyes were reviewed. Polypoidal lesions in the choroidal vasculature were detected in

Figure 1 (A) Preoperative panoramic fundus photograph of a 74-year-old man (patient 3) with a massive subretinal haemorrhage (SRH) and bullous retinal detachment involving the two inferior quadrants. The visual acuity is 20/1000. (B) Indocyanine green angiogram obtained 1 month before the onset shows a branching network of vessels and polypoidal or aneurysmal dilation at the end of the network. (C) Intraoperative view shows accumulation of the liquefied subretinal clot at the posterior pole in a gravity-dependent manner. (D) Intraoperative view shows displacement of the SRH to the periphery after intravitreal injection of perfluorocarbon liquid. (E) Panoramic fundus photograph 1 month after surgery shows complete removal of the SRH and retinal reattachment, with visual acuity improvement to 20/60. (F) Fundus photograph after vitrectomy with silicone oil tamponade for management of recurrent SRH shows a defect of the retinal pigment epithelium layer from the macula to the temporal side with a visual acuity decrease to 20/1000.

Table 1 Patient data

Number	Sex	Age	Eye	SRH			Macular involved	Presence of PCV	VA			
				Duration (days)	Area (quadrants)				Preop	Postop best	Final	Follow-up (months)
1	M	64	RE	14	4		Yes	Unknown	HM	20/100	20/200	36
2	M	71	RE	7	4		Yes	No	HM	20/100	20/400	32
3	M	74	LE	2	2		Yes	Yes	20/1000	20/60	20/1000	26
4	F	52	LE	12	3		Yes	Yes	20/400	20/200	20/200	24
5	M	60	LE	21	4		Yes	Yes*	CF	20/200	20/200	21
6	M	70	RE	10	3		Yes	Yes	20/200	20/40	20/60	17
7	M	84	LE	9	3		Yes	No	HM	20/100	20/250	14
8	M	91	RE	7	4		Yes	No	LP	20/400	20/400	12

CF, counting fingers; F, female; Final, VA measured at the most recent follow-up visit; HM, hand motions; LE, left eye; LP, light perception; M, male; PCV, polypoidal choroidal vasculopathy (defined as presence of polypoidal lesions in choroidal vasculature); Postop, postoperative; Preop, preoperative; RE, right eye; SRH, subretinal haemorrhage; VA, visual acuity.

*Polypoidal lesions were present in the fellow eye.

the affected eyes in 3 (43%) patients before or after the onset of the haemorrhage (figs 1, 2) and in the fellow eye in one patient.

Preoperative visual acuity varied from light perception to 20/200. The best visual acuity after surgery ranged from 20/200 to 20/40. Vision improved by 0.3 logMAR unit or more in all eyes, with 2 (25%) eyes having visual acuity 20/60 or better (fig 4A). The final visual acuities ranged from 20/1000 to 20/60 and improved in 7 (88%) eyes; in one patient, the visual acuity was unchanged from that observed preoperatively (fig 4B). The final visual acuity reached 20/400 or better in 7 (88%) eyes; 1 (13%) eye had visual acuity 20/60 or better. The visual acuity tended to decrease with long-term follow-up; the final visual acuity was worse by ≥ 0.3 logMAR unit than the best postoperative visual acuity in 4 (50%) eyes and essentially unchanged in the other four eyes. Preoperative and postoperative visual acuity levels were analysed using the signed rank test. Significant differences were found between the preoperative and best postoperative visual acuity levels ($p = 0.011$) and between the preoperative and final postoperative visual acuity levels ($p = 0.018$).

No vision-threatening complications attributable to surgery were observed. One eye required secondary implantation of an intraocular lens because the crystalline lens was removed during the initial surgery. A large submacular haemorrhage recurred in one eye 14 months after the initial surgery and was successfully treated with vitrectomy and silicone oil tamponade (fig 1). However, the visual acuity after treatment gradually decreased to 20/1000 at the final examination.

DISCUSSION

The therapeutic principle of the current newly modified procedure is based on two synergistic effects: pharmacologically induced subretinal haemolysis by intravitreal tPA and subsequent mechanical drainage of liquefied blood assisted by perfluorocarbon liquid intraoperatively and by gas tamponade postoperatively. The treatment sequence performed in the current study has several theoretical advantages. Intravitreal injection of tPA between 12 and 24 h preoperatively seems to play a key role in the procedure. We showed previously that a fresh SRH can be displaced by gas tamponade alone.¹⁴ However, solid blood clots present for >1 week might not be displaced without using a chemical adjuvant such as tPA. In the current study, most patients had had the SRH for >7 days, so they received an intravitreal injection of 25 μ g of recombinant tPA 12–24 h preoperatively to facilitate maximum clot liquefaction. Despite the relatively long duration and massive volume of the SRHs in our series, we treated our patients with only 25 μ g tPA compared with the 50–100 μ g used in recent studies, because of concern about retinal toxicity.^{12–13 19 20} At 12–24 h after injection, clot liquefaction was detected as caused by changes in the echographic configurations of the haemorrhagic retinal detachment with eye movement by preoperative B-scan examination (figs 2, 3). During vitrectomy, complete clot liquefaction was observed as a gravity-dependent accumulation of SRH at the posterior pole (fig 1). Diffusion of intravitreal tPA into the subretinal spaces is not well understood. Although Kamei *et al* reported that intravitreal tPA did not diffuse into the subretinal spaces in normal rabbits,²¹ there is much evidence that intravitreally injected tPA migrates across the pathologic retina.^{22–26} Retina damaged by SRH, in contrast with a normal retina, might have microlesions allowing bidirectional diffusion; subretinal haemorrhage flows into the vitreous cavity and intravitreal tPA diffuses into the subretinal spaces and vice versa.^{13 23} In humans, injection of 50 μ g tPA seems to be sufficient for haemolysis, causing an inferior shift of the SRH in a gravity-dependent manner.²⁶ However, intravitreal injection of ≥ 50 μ g tPA induced retinal toxicity—that is, retinal necrosis

Figure 2 (A) Preoperative panoramic fundus photograph of a 52-year-old woman (patient 4) with a massive subretinal haemorrhage (SRH), haemorrhagic pigment epithelial detachment, and haemorrhagic retinal detachment extending to three quadrants. The visual acuity is 20/400. (B) Indocyanine green angiogram shows dilation of the choroidal vascular network (arrows), indicating the presence of polypoidal lesions. (C, D) B-scan echography 18 h after injection of intravitreal tissue plasminogen activator shows changes in the echographic configurations of the haemorrhagic retinal detachment with eye movement, suggesting complete liquefaction of the clotted SRH. (E) Panoramic fundus photograph 1 month after surgery shows complete removal of the SRH and retinal reattachment, with improvement of visual acuity to 20/200. (F) The visual field is preserved with minimum damage to the previously detached retina and the underlying RPE.

and exudative retinal detachment.^{13–20} With the appropriate dose of tPA (25 µg), we did not encounter any retinal pigmentary changes or vision loss in our patients.

Our technique is also advantageous because there is no need for extensive and potentially traumatic manipulations and large retinotomies to remove the clotted SRH. Surgical removal of

submacular haemorrhages, even use of tPA, has been associated with various complications, including retinal detachment, proliferative vitreoretinopathy, macular holes and epiretinal membrane proliferation.^{5–10, 18–27} Direct subretinal tPA irrigation during vitrectomy often only achieves partial clot lysis. Submacular manipulation via posterior retinotomy is

Figure 3 (A) Preoperative panoramic fundus photograph of a 91-year-old man (patient 8) with a massive subretinal haemorrhage (SRH), choroidal haemorrhage and haemorrhagic retinal detachment extending to four quadrants. The visual acuity is light perception. (B, C) B-scan echography 24 h after intravitreal injection of tissue plasminogen activator shows changes in the echographic configuration of the haemorrhagic retinal detachment with eye movement, suggesting liquefaction of the clotted subretinal and choroidal haemorrhage. (D) Panoramic fundus photograph 12 months after surgery shows complete resolution of the SRH and retinal reattachment without recurrence. Despite a large defect in the RPE layer including the macular region, the visual acuity improved to 20/400.

Figure 4 (A) Best postoperative visual acuity plotted against the preoperative visual acuity in eight eyes. The open triangles represent the patients who had a massive subretinal haemorrhage for <7 days. (B) Final visual acuity plotted against preoperative visual acuity. The open circles represent the patient with a recurrent subretinal haemorrhage. CF, counting fingers; HM, hand motions; LP, light perception.

then required to remove the subretinal clot, and inadvertent manipulation may eventually lead to enlarging the retinotomy. In our series, no complications were directly attributable to the surgical procedures. On using tPA preoperatively and gently forcing the SRH after an overnight, pharmacologically induced haemolysis reduced the risk of retinal toxicity compared with a direct dose of subretinal tPA, and avoided retinal and RPE damage compared with direct subretinal manipulation. Although draining additional liquefied blood from the anterior chamber was required in some patients, removing it at the bedside was convenient and much safer than intraoperative subretinal manipulation. Peripheral retinotomy seems to be more advantageous than posterior retinotomy to displace the additional liquefied subretinal blood migrating into the vitreous cavity after overnight prone positioning and gas tamponade. Retinal detachment is a serious postoperative complication sometimes resulting from reopening of the posterior retinotomy, because the underlying fibrotic changes may impair the retina-RPE adhesion. Therefore, creating small retinotomies in the periphery without underlying pathology but not in the posterior might be essential for avoiding postoperative complications in our patients.

The overall visual outcomes in our series were much better compared with the natural history of massive SRHs associated with AMD.⁴ The initial visual results were encouraging, with all

eyes improving and with 5 (63%) eyes achieving a visual acuity of 20/100 or better (table 1). Most patients had improved vision, especially in the visual fields, soon after the haemorrhage was removed from the subretinal spaces and after successful repair of the haemorrhagic retinal detachment. During the mean follow-up of 23 months, the final visual acuity was worse by ≥ 0.3 logMAR unit than the best postoperative visual acuity in 4 (50%) eyes because of progression of the underlying pathology at the macula. Nevertheless, a comparison of our data with previously published studies on surgical evacuation of massive SRHs suggests possible benefits.⁵ In the current study, 7 of 8 (88%) eyes had final visual acuity levels of 20/400 or better after one surgery. A review of recent studies showed that only 64% (7/11) of patients achieved a final visual acuity of 20/400 or better, suggesting that our procedure may result in similar and better visual outcomes compared with recently reported surgical procedures.^{17–18, 27}

A gradual decrease in visual recovery and recurrence of haemorrhages are postoperative trends observed in a variety of treatments for removing SRH.^{5, 7, 8, 10, 13, 27} The presence and progression of underlying pathology including degenerative RPE changes seem to account for the visual decrease and recurrence of the SRH. AMD is the disease that most often causes massive SRHs.^{4, 5, 16–18} In contrast, a review of angiographic findings in our patients showed that polypoidal lesions in the choroidal vasculature are often present in patients with massive SRHs. Although retinal manifestations of polypoidal choroidal vasculopathy (PCV) resemble those of neovascular AMD, the clinical entity, demographic features and pathologic characteristics are distinct.^{28, 29} Thick and recurrent submacular haemorrhage is a well-known macular manifestation associated with PCV and has a high incidence in Japanese patients.^{29–31} However, massive SRHs complicated with large haemorrhagic retinal detachments have never been associated with PCV.

To the best of our knowledge, this is the first study to report that PCV may be another cause of massive SRH. At present, we cannot comment on the degree to which AMD and PCV contribute to massive SRH, because of insufficient data for analysis and the retrospective nature of our study. A controlled study with a large population is necessary to clarify this issue.

The limitations of the present study are its retrospective nature, the small sample size, lack of a control group and non-standardised protocols for visual acuity measurement and follow-up care. More research and a large, prospective, randomised clinical trial with a control group would determine the benefits of this surgery. However, because no proposed treatment exists that consistently results in improved vision in patients with massive SRH, preoperative intravitreal injection of tPA followed by vitrectomy with peripheral retinotomy may be a useful alternative for managing this complication.

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