SCIENTIFIC REPORT

Management of subretinal macular haemorrhage by direct administration of tissue plasminogen activator

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Background/aims: Recent studies on the treatment of acute subretinal macular haemorrhage have shown that the volume of the clot and the time to evacuation have strong prognostic factors for visual outcome. A novel technique for surgical evacuation of these lesions involves direct injection of tissue plasminogen activator (t-PA) into the haematoma using pars plana vitrectomy. The aim of this study was to evaluate the clinical outcomes of this recently described procedure.

Methods: 17 consecutive patients with subretinal macular haemorrhages caused by age related macular degeneration were enrolled. Patient demographics, acuities, and fluorescein angiograms were obtained for all evaluations. All patients underwent complete three port pars plana vitrectomy to enable direct cannulation of the subretinal space and injection of 48 μg of t-PA, partial fluid-air exchange, 1 hour face up supine positioning postoperatively, followed by upright positioning overnight.

Results: 88% of patients within the study had stabilisation or improvement of visual acuity. Nine patients had total clearing of the macular haemorrhage and eight patients had subtotal clearing. Two patients had recurrence of the haemorrhage after the procedure and one patient underwent repair for retinal detachment. Occult lesions demonstrated similar outcomes to classic or predominately classic lesions. Nine patients required no therapy after the study to treat subfoveal neovascularisation.

Conclusions: This study represents one of the largest case series to date showing that direct injection of subretinal t-PA with air-fluid exchange only and no intraoperative clot lysis period can have favourable results.

Subretinal macular haemorrhage is a common manifestation of choroidal neovascularisation secondary to age related macular degeneration. When it involves the central macular area, it represents a severe threat to visual acuity while also hindering possible therapeutic interventions such as measurement of lesion size, administration of photodynamic therapy, or use of focal laser photocoagulation. It has been well established that the natural prognosis of submacular haemorrhage is very poor.[1–4] This is the result of a barrier effect that prevents metabolic exchange between the retina and choriocapillaris, toxicity of iron released by the haemoglobin, and shearing of the outer segments of the photoreceptors from contraction of the haemorrhage.[5–7] The prognosis of submacular haemorrhage is further worsened if the haemorrhage is thick and is associated with age related macular degeneration.[2]

Several therapeutic procedures have been employed to improve results. In early studies, attempts were made with vitreoretinal surgery involving the creation of a retinotomy to directly evacuate the haemorrhage using a subretinal irrigator/aspirator.[8–12] Results were disappointing, most probably secondary to surgically induced retinal and/or retinal pigment epithelial damage. Over the past decade, evacuation of haemorrhage with intraocular recombinant tissue plasminogen activator (t-PA) offered the benefit of reducing the barrier formed by the haemorrhage impeding metabolic exchange, diluting the toxic factors released by red blood cells, and lysing the inter-photoreceptor fibrin.[7 13–17]

Heriot *et al* were able to demonstrate that intravitreal injection of t-PA and perfluoropropane (C_3F_8) gas displaces the haemorrhage with postoperative positioning for 1–3 days.[18] This method has come to be known as pneumatic displacement. It is believed that stretching of the retina from the subretinal haemorrhage may induce microlesions allowing for diffusion of the t-PA into the subretinal space.[19] Whether sufficient quantities of t-PA penetrate the retina to cause dissolution of the subretinal clots is questionable and recent animal studies have reiterated this concern.[20 21] Lewis *et al* have shown that displacement of subretinal clot without previous liquefaction and pneumatic displacement can cause irreversible photoreceptor damage.[22]

To ensure adequate delivery of t-PA to the subretinal clot, Haupert *et al*[23] proposed a technique which hybridised the use of subretinal t-PA and pneumatic displacement by directly injecting t-PA into the subretinal haemorrhage, followed by haemodisplacement by fluid-air exchange and postoperative upright positioning. This technique offers the advantages of ensured t-PA exposure to the blood clot and minimal manipulation of the retina resulting in nominal trauma. The initial experience suggested a high anatomical success rate, with blood displacement in all 11 cases and few complications. However, the study variability of surgical technique among the surgeons involved called into question the validity of the results. A recently published study by Olivier *et al* using a similar procedure also showed promising results.[24] The purpose of this study is to further investigate the efficacy of treating submacular haemorrhage with direct t-PA injection without an intraoperative clot lysis time and without injection of an expansile gas.

Methods

Consecutive surgically treated patients with subretinal haemorrhage involving the foveal centre were investigated. All haemorrhages were secondary to age related macular degeneration and did not extend beyond the vasculature arcades. The surgical procedures were all performed by a single surgeon (JS) between May 2000 and July 2005. An informed consent form was signed by each patient before surgery. Institutional review board approval was obtained for this study.

A standard three port pars plana vitrectomy was performed and a posterior vitreous detachment was created if not already present. Using a microcanula, a small retinotomy was created just outside the blood clot to act as an infusion site.

Abbreviations: C_3F_8, perfluoropropane; t-PA, plasminogen activator

Table 1 Summary of patient data

Average patient age (SD)	81.1 (7.1) years
Submacular haemorrhage duration (SD)	11.9 (11.6) days
Average follow up	17.2 months
Subfoveal blood displacement postoperatively	
Total displacement	9
Subtotal displacement	8
No displacement	0
Postoperative fluorescein findings	
Classic	2
Predominately classic	4
Minimally classic	2
Occult	9
Postoperative complications	
Rebleed	3
Retinal detachment	1
None	13
Postoperative treatments	
Focal laser	1
Photodynamic therapy	5
Scleral buckle/vitrectomy	1
Pegaptanib sodium injection	1
None	9
Coumadin use	
Yes	6
No	11

Then, a 32 gauge rigid cannula was used to infuse t-PA (Activase, Genentech Inc, South San Francisco, CA, USA) into the subretinal space creating a bullous retinal detachment encompassing the entire blood clot. A t-PA dosage of 12 μg per 0.1 ml was used in each case, with a total dose of 48 μg administered. Two important surgical points were observed. Firstly, care was taken to inject into the clot with a 32 gauge cannula, not between the clot and the retina, to avoid stripping the clot from the photoreceptors. Secondly, the retinotomy was kept small so as to be nearly self sealing even under fluid. A fluid-air exchange was then performed to the dome of the macular detachment. All patients were placed for 1 hour face up, and then sat upright overnight.

Demographical data including age, sex, best preoperative corrected Snellen visual acuity, best and final postoperative corrected Snellen visual acuity, duration of haemorrhage, postoperative fluorescein angiography, any postoperative treatments or complications, whether patient was medicated with coumadin at time of haemorrhage, and duration of postoperative follow up period were recorded for each patient. Total subfoveal haemorrhage displacement was defined as the absence of blood in the foveal area as determined by early postoperative fundal examinations and fluorescein angiography; subtotal displacement was defined as a reduction in the amount of subfoveal blood, but with some blood remaining in the fovea postoperatively.

RESULTS

Demographic data are given in table 1. Seventeen patients were enrolled in the study. There were nine females and eight males with a mean age of 81.1 years (range 63–96). The mean submacular haemorrhage duration before surgery was 11.9 days (range 1–50 days). The mean follow up was 17.2 months (range 3–48 months).

Tables 2 and 3 summarises the visual acuity achieved before and after surgery and stratified to type of lesion. Preoperative visual acuity ranged from 20/70 to light perception. Best postoperative visual acuity ranged from 20/25 to counting fingers at 2 feet, with 13 eyes better than 20/200 and improvement was made in all but five patients. Of these five, the visual acuity in two eyes worsened and in the other three eyes remained the same.

DISCUSSION

In this study we evaluated the efficacy of direct subretinal t-PA injection followed by air pneumatic displacement in the treatment of submacular haemorrhage secondary to age related macular degeneration. All patients underwent pars plana vitrectomy, direct t-PA injection into the subretinal space creating a neurosensory retinal detachment that encompassed entire haemorrhage, and fluid-air exchange followed by postoperative positioning. The subretinal injection of t-PA into the haemorrhage allowed for the entire clot to bathe in the fibrolytic solution, permitting the adequate clot liquefaction necessary for successful pneumatic displacement without injury to the retina. There was no observed intraoperative waiting period for clot lysis. Clot displacement was achieved with fluid-gas exchange, supine positioning for 1 hour, and postoperative upright positioning overnight.

The toxicity of arginine, the carrier for t-PA, to the retina and retinal pigment epithelium has been established in numerous studies.[25–28] We chose to use a 48 μg dose of t-PA in all our cases. This amount was sufficient to engulf the subretinal clots, and was within the 50 μg dose that Lewis *et al* found safe in the rabbit model.[7] We found no evidence of retinal toxicity secondary to t-PA in any of our patients.

A significant number of patients required no postoperative treatment of neovascular complexes. Owing to the sample size of the study, there was no clear determination whether a specific lesion type led to quiescence of the neovascular membrane or better visual outcomes. The majority of patients

Table 2 Visual acuity after submacular haemorrhage removal

Visual acuity	Preop/postop VA (%)
Light perception/count fingers/hand motion	47.1/23.5
20/400–20/200	41.2/23.5
>20/200	11.8/52.9

Table 3 Visual acuity with respect to lesion type

	Preop/postop VA (%)	
Visual acuity	Occult	Classic/predominantly classic
Light perception/count fingers/hand motion	37.5/37.5	57.1/14.3
20/400–20/200	50.0/0.0	42.9/28.6
>20/200	12.5/62.5	0.0/57.1

who had submacular haemorrhage harboured occult only membranes which did not demonstrate leakage by fluorescein angiography after displacement of the haematoma. Further studies are indicated to determine whether the procedure itself accounts for converting these lesions into stable, non-leaking complexes or whether this is the natural history of lesions that bleed acutely in patients with exudative age related macular degeneration.

There are many clear advantages of this surgical procedure in comparison with current methods used to treat submacular haemorrhage. Surgical trauma to the retina and retinal pigment epithelium is minimised because other than a small retinotomy used for injection of t-PA into the subretinal space, there is no manipulation of these tissues. The liquefied haemorrhage is then pneumatically displaced away from the macula. Other procedures attempt to extract the subretinal t-PA and liquefied blood, which exposes the retina to mechanical stresses that can easily lead to injury. This case series also highlighted that the 60 minute intraoperative waiting period for clot lysis when using subretinal t-PA is unnecessary. Furthermore, there was only pneumatic displacement with air and not conventional expansile gases leading to fewer complications during the postoperative period associated with intraocular gas such as increased pressure and cataract formation. Given the success rate without expansile gas injection, this study further validates the results of Olivier and colleagues and Awh, the originator of this concept.[29] While this technique is technically more difficult than previous methods reported, this study supports the notion that subretinal t-PA and air-fluid exchange is the safest and most effective management for macular haemorrhages. Larger clinical trials would be helpful in determining if lesion type relates both to better anatomical outcome and visual success.

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