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Research Article

Pneumatic Displacement with Intravitreal Plasminogen Activator (PA) versus Vitrectomy with Subretinal PA for Submacular Haemorrhage

Ching J[1,4]†, Cardoso J[2]†, Cabrera RG[2], Grabowska A[2], Karia N[2], Saidkasimova S[1]‡* and Chandra A[2,3]‡*

[1]Norfolk and Norwich University Hospitals, Colney Lane, Norwich, NR4 7UJ, UK

[2]Southend University Hospital, Prittlewell Chase, Essex, SS0 0RY, UK

[3]Vision and Eye Research Unit, Anglia Ruskin University, Cambridge, UK

[4]John Van Geest Centre for Brain Repair, E.D. Adrian Building, Cambridge, CB2 0PY, UK

†Authors contributed equally

‡Authors contributed equally

***Corresponding author:** Mr Aman Chandra, Department of Ophthalmology, Southend University Hospital, Prittlewell Chase, Southend on Sea, SS00RY, Essex, Vision and Eye Research Unit, Anglia Ruskin University, Cambridge, United Kingdom

Miss Shohista Saidkasimova, Department of Ophthalmology, Norfolk and Norwich University Hospitals, Colney Lane, Norwich, NR4 7UJ, UK

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Abstract

Introduction: To compare the efficacy of pneumatic displacement with intravitreal recombinant tissue plasminogen activator (rTPA) [Group 1] versus vitrectomy with subretinal injection of rTPA with/without anti-VEGF [Group 2] for submacular haemorrhage (SMH) in patients with neovascular age-related macular degeneration (nAMD) in two tertiary referral centres.

Methods: Retrospective analysis of thirty consecutive patients presenting with SMH and treated with the aforementioned regimens in two surgical units between 2012 to 2016. Primary outcome measure was SMH displacement. Secondary outcomes included best-corrected visual acuity (BCVA) change post-operatively, SMH height, SMH area, and surgical complications. Optical coherence tomography (OCT) images and clinical data used to analyse outcomes.

Results: Eleven patients included in Group 1 and 19 in Group 2. Haemorrhagic displacement was complete in 9 (82.8%) out of 11 and 18 (94.7%) out of 19 patients in Groups 1 and 2, demonstrating no difference between them (p=0.536). BCVA improved by -0.50±0.74 (p=0.045) and -0.72±0.93 (p=0.004) compared to baseline at 6 months in Groups 1 and 2, with no difference between groups (p=0.155). Subfoveal haemorrhage height reduced (Group 1:-900.57μm, p=0.007; Group 2:-607.27μm, p<0.001), without difference between groups (p=0.582). SMH area reduced significantly in Group 2 but not 1 (Group 1:-44.18μm, p=0.078; Group 2:-30.28μm, p<0.001), without difference between groups (p=0.913).

Conclusion: Intravitreal treatment and vitrectomy were equally effective at subfoveal haemorrhagic displacement. BCVA gains did not differ significantly between techniques. OCT data demonstrated similar efficacy in both techniques. This data supports the use of either intravitreal or vitrectomy treatment as a first line therapy for SMH.

Keywords: Subretinal haemorrhage; Neovascular age-related macular degeneration; Anti-vascular endothelial growth factor; Tissue plasminogen activator; Pneumatic displacement; Gas

Introduction

The natural history of submacular haemorrhage (SMH) portends a poor visual prognosis and is often associated with neovascular age related macular degeneration (nAMD), though many aetiologies exist [1-3]. The Submacular Surgery Trial demonstrated that physical removal of blood through a posterior pole retinotomy did not improve best corrected visual acuity (BCVA) [4]. Several mechanisms for retinal toxicity secondary to SMH have been proposed, where animal experiments have shown a barrier effect by fibrin infiltration created by SMH prevents choroidal perfusion of the neurosensory retinal layers [5-7]. Further mechanisms include direct toxic effect on photoreceptor function from haemolytic products iron and hemosiderin [8-11].

As a result, a number of treatment strategies to overcome SMH have been proposed, including anti-vascular endothelial growth factor (VEGF) intravitreal injections alone or in combination with techniques to mechanically displace the SMH [12-15]. Pneumatic displacement of submacular haemorrhage with expansile gas was first introduced in 1996 and has subsequently been shown to result in visual gains over the natural history of SMH [A,16,17]. Thereafter, attempts to improve efficacy by combining intravitreal expansile gas with intravitreal rTPA have been shown to result in complete haemo-displacement in 73% of patients (n = 192) [16]. Hillenkamp and colleagues went on to demonstrate in 47 patients that subretinal rTPA with vitrectomy was more effective than intravitreal rTPA, thus paving the way for development of a variety of surgical regimens that include subretinal anti-VEGF [8,18,19].

In the present study, we sought to compare two groups of patients that underwent less invasive intravitreal treatment and more invasive vitrectomy assisted haemodisplacement techniques for SMH as a complication of nAMD. Each technique has been shown

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to have efficacy in a number of independent studies [16,19]. Recent comparative studies have not shown either of these techniques to be superior in haemodisplacement or visual outcome [20-22].

Herein we present a retrospective non-randomised comparative case series of consecutive patients treated with pneumatic displacement versus vitrectomy assisted displacement in two centres serving a similar geographic area.

Methods and Materials

All patients with SMH secondary to nAMD treated in two centres from 2012 to 2016 were retrospectively recruited to the study. Inclusion criteria were: fovea involving SMH with sudden onset of reduced vision worse than 6/36; area at least two disc diameters and duration no more than 45 days in group 1 and no more than 14 days in Group 2. Exclusion criteria were pre-existing comorbidity including underlying extensive subretinal fibrosis/ geographic atrophy and SMH caused by pathologies other than nAMD. This study adhered to the tenets of Declaration of Helsinki. Full consent was obtained as standard from every patient prior to proceeding to surgery.

Patients were divided into two groups: Group 1 received intravitreal pneumatic displacement (sulfahexafluoride [SF6] or hexafluoroethane [C2F6] gas) and intravitreal rTPA with/without intravitreal anti-VEGF and Group 2 received pars plana vitrectomy in combination with subretinal rTPA, with/without subretinal Anti-VEGF, with SF6 gas tamponade.

The main outcome measure was haemo-displacement. This was defined as complete if all foveal blood was displaced, partial if some blood remained in the sub foveal region and incomplete if blood remained at the fovea, at 1 months review, as described elsewhere [19]. Secondary outcomes included BCVA, the number of pre- and post-operative anti-VEGF injections, SMH height, SMH area and surgical complications.

Patient assessment pre- and post-operatively included Snellen best corrected visual acuity, macular optical coherence tomography (Topcon OCT-2000, Topcon Corporation, Tokyo, Japan; RTVue-100 FD-OCT, Optovue Inc. Fremont, CA, USA; HRA Spectralis, Heidelberg Engineering, Heidelberg, Germany), tonometry, anterior segment and dilated fundus slit lamp examination. Co-morbidities and regular medication was recorded for each patient.

For analysis, BCVA was converted to logarithm of minimum angle of resolution (LogMAR) values [23]. OCT images were analysed by taking the Central Retinal Thickness and Average Retinal Volumes calculated by the Topcon OCT mk. III, the RTVue-100 and Heidelberg Engineering HRA Spectralis softwares. SMH height was measured from the base of the haemorrhage to the first photoreceptor layer at the fovea and at the maximum height of the haemorrhage. The area of SMH was outlined using the analysis function on the Topcon imaging system as described previously and applied to the Heidelberg Spectralis and RTVue-100 area measurement function [18].

Surgical technique

Group 1: Pneumatic displacement was performed with intravitreal injection of 50mcg/0.1ml of rTPA (Actilyse® Boehringer, Ingelheim) diluted to above concentration) and an intravitreal injection of an undiluted expansile concentration of SF6 (0.5ml) or C2F6 (0.3ml) according to surgeon preference. In some patients, an intravitreal injection of 1.25mg/0.05ml of Bevacizumab (Avastin, Genetech, San Francisco, USA) was used after the intravitreal rTPA, according to surgeon preference. Patients were postured supine for 30 minutes followed by face down posture for 3 days. Patients were reviewed at day one, when a decision regarding further intervention (pars plana vitrectomy assisted displacement) was taken. They were then reviewed at 2 weeks, and subsequently every 4-6 weeks according to the anti VEGF treatment regime.

Table 1: Summary of demographics and outcome measures.

	Group 1	Group 2	
Number	11	19	-
Baseline characteristics			
Age	84.27 ± 2.69	82.93 ± 8.14	0.602
Male	6 (54.5%)	9 (47.40%)	0.957
Female	5 (45.5%)	10 (52.60%)	0.527
ARMD underlying diagnosis	11 (100%)	19 (100%)	-
No. Anti-VEGF injections before presentation	1.18 ± 1.78	5.72 ± 10.98	0.181
Pseudophakic at time of surgery	4 (36.436%)	8 (42.10%)	0.825
Warfarin	2 (18.18%)	0 (0.00%)	0.064
Aspirin/Clopidogrel	6 (54.54%)	4 (21.10)%	0.08
Haemorrhage height at fovea pre-operatively (μm)	1119.71 ± 830.78	801.84 ± 375.49	0.185
Maximum haemorrhage height pre-operatively (μm)	1340.43 ± 679.35	944.11 ± 305.68	0.052
Haemorrhage area pre-operatively (μm^2)	50.80 ± 58.28	37.90 ± 16.63	0.389
LogMAR VA at presentation	1.47 ± 0.52	1.86 ± 0.59	0.092
Post operative			
No. Anti-VEGF injections post-operatively	2.27 ± 1.90	4.71 ± 7.05	0.276
Complete displacement	9 (81.81%)	18 (94.70%)	0.536
LogMAR VA at 1 month Follow-up	1.22 ± 0.65	1.29 ± 0.69	0.804
LogMAR VA at 3 month Follow-up	0.95 ± 0.6	1.03 ± 0.62	0.743
LogMAR VA at 6 month Follow-up	1.05 ± 0.65	1.02 ± 0.68	0.897
Days between onset and presentation	10.64 ± 14.21	2.00 ± 2.59	0.017
Days between presentation and surgery	6.82 ± 8.38	6.06 ± 9.37	0.813
Days between onset and surgery	17.45 ± 13.82	8.06 ± 8,91	0.037
Complications	2 (18.18%)	2 (10.52%)	0.871

Group 2: All patients underwent 23 gauge three port vitrectomy under local anaesthetic as a day case. After core and peripheral vitrectomy 0.05ml of ranibizumab (Lucentis) and 0.05ml of 25mcg/ml rTPA (Actilyse® Boehringer, Ingelheim) diluted to above concentration in hospital pharmacy) and 0.05ml of ranibizumab (Lucentis) (if patient met local Clinical Commissioning Group criteria) was injected into the subretinal space using 41 gauge cannula (DORG). Injection site selected at the highest point of SMH taking into account desirable direction of displacement of haemolysed blood away from fovea. Care was taken to inject slowly to avoid over inflation and break through the fovea". Fluid-air exchange with 22% SF6 gas injection was carried out at the end of procedure. Patients were postured supine for an hour followed by upright or on their temporal side posture depending on the direction of intended

displacement of SMH for 3 days.

Patients were reviewed at 2 weeks, post-operatively and every 4-6 weeks thereafter. All patients received on going treatment with intravitreal anti-VEGF.

Statistics

Appropriate descriptive and comparative statistical analysis was undertaken using GraphPad Prism 7, GraphPad Software Inc., California, for Mac. Statistical significance was considered a p value of <0.05.

Results

Thirty patients were included in the study. Fourteen and 16 patients were treated at the SUH and NNUH, respectively. Eleven patients were allocated to Group1 and 19 to Group 2. Patient baseline characteristics are summarised in Table 1.

Haemorrhagic displacement was complete in 9 (82.8%) out of 11 and 18 (94.7%) out of 19 patients in Groups 1 and 2, demonstrating no difference between the groups (p = 0.536), summarised in Table 2.

BCVA at 1, 3 and 6 months follow up were collected as summarised in Table 1, with improvement shown in Graph 1. BCVA improved by -0.50 ± 0.74 (p = 0.045) and -0.72 ± 0.93 (p = 0.004) from baseline to last follow up within 6 months in Groups 1 and 2 respectively, however comparison in BCVA change between groups did not reach statistical significance (p = 0.217), summarised in Table 2. OCT data demonstrated significant reductions in subfoveal haemorrhage height (Group 1: -900.57μm, p = 0.007; Group 2: -607.28μm, p < 0.001) and maximum SMH height (Group 1: 611.57μm, p = 0.006; Group 2: -627.41m, p < 0.001) post-operatively in both groups, demonstrating no difference between them (p = 0.582 and 0.136 respectively). SMH area reduced significantly in Group 2 but not 1 (Group 1: -44.18μm, p = 0.078; Group 2: -30.28μm, p <0.001), with no difference between groups (p = 0.913).

Post-operative Anti-VEGF intravitreal injections were given an average of 2.27 ± 1.90 and 4.49 ± 7.22 times in Groups 1 and 2 respectively. Two (18.2%) post-operative complications occurred in Group 1: with one patient having a further SMH and another a vitreous haemorrhage. Two (10.5%) patients had complications in Group 2: one having retinal pigment epithelial rip and a further patient having a suprachoroidal haemorrhage with ocular hypertension and retinal detachment.

Discussion

The main finding of this study are that intravitreal and vitrectomy assisted SMH displacement techniques are similarly efficacious, in keeping with the most recent comparative studies [20,22]. We note that de Jong and colleagues [20] attempted to quantify haemorrhage displacement by measuring the haemorrhage volumetric change on spectral domain OCT whereas Fassbender and colleagues [22] measure the final disciform scar. Although we have not sought to quantify haemorrhage displacement, our results come to the same conclusions as both these studies and with literature reviews to date [16,19]. Visual acuity improvements for both techniques have been found to be significant and similar between interventions in the present study, in accordance with other comparative studies [20-22].

Table 2: Statistical summary of key outcomes.

Complete Displacement	Group 1	Group 2
	N=11	N=19
No	2 (18.2%)	1 (5.3%)
Yes	9 (81.8%)	18 (94.7%)
P-value (Fisher's Exact test)	0.5367	
Change in logMAR BCVA(month 6 - initial)	-0.5 (0.73) [n=11]	-0.72 (0.93) [n=18]
95% Confidence Interval	-0.9900 to -0.0118	-1.1797 to -0.2560
P-Value (Paired t-test)	0.045	0.0044
Difference between treatments in Change log MAR BCVA	0.217	
95% Confidence Interval	-0.4583 to 0.8922	
P-value (Two sample t-test)	0.5153	

Highly significant and favourable OCT changes were found to be comparable between interventions, in keeping with literature to date.

The treatment of SMH is controversial, with reports of efficacy with monotherapy anti-VEGF treatment [14,24], pars plana Vitrectomy with subretinal rTPA [10,12,18], and expansile gas displacement [17,25,26]. There are some suggestions that vitrectomy with subretinal therapy is associated with greater visual gains post-operatively compared to intravitreal treatment regimens, but these are unsubstantiated as yet [16]. Equally, this treatment requires a more invasive procedure and may be associated with more complications [16]. Intravitreal triple therapy in comparison is associated with a better final visual outcome, quite possibly because SMH size may be less than those treated with vitrectomy [15,16,27-29]. However, since no "Gold Standard" treatment regimen has emerged, uncertainty remains regarding relative efficacy of all these methods, and in particular whether less invasive intravitreal treatment is directly comparable to vitrectomy. The present study attempts to add further evidence for the role of vitrectomy compared to intravitreal therapy by comparing two patient groups treated at two tertiary centres in the same region.

All preoperative demographic characteristics were similar apart from the number of days between onset and surgery as shown in Table 1. A sub analysis excluding patients where SMH existed longer than 14 days from onset to surgery (5 patients from Group 1 and 1 patient from Group 2) demonstrated no significant difference between Groups and all outcomes (data not shown). This therefore allows us to draw meaningful comparisons between the two groups of patients.

Herein we demonstrate no difference in haemo-displacement between intravitreal and subretinal treatment with vitrectomy for SMH. Our rates of haemo-displacement are in keeping with previous literature [19]. This supports collated evidence presented by van Zeeburgh et al. and Stanescu-Segall et al., adding impetus to the need for a RCT comparing the two treatment modalities [16,19].

Group 1 benefitted from -0.50 LogMAR BCVA improvement at last follow up within 6 months (n = 11). This compares well to a combined analysis performed on studies using gas and TPA demonstrated equivalent LogMAR BCVA gains of approximately -0.4, or from 20/756 to 20/200, at final review (n = 206) [16,17,25].

In this series of studies, the average SMH size was 4.3 disc diameters, smaller than the 50.80mm^2 in our study. The comparatively smaller sample in Group 1 may partly account for the lower level of BCVA gained.

Our analysis revealed greater BCVA gains in patients receiving vitrectomy, but this did not reach statistical significance between treatment groups. Our data disagrees with some suggestions that BCVA gains are greater with vitrectomy and that intravitreal treatment supersedes final BCVA of vitrectomy [16]. However, it should be appreciated that with a limited sample size and differences between intravitreal anti-VEGF protocols for nAMD at the two units, these differences should be interpreted with caution. In addition, there was also a significant difference in time between onset and surgery between Groups 1 and 2, which may have affected final visual outcome, although interestingly did not affect displacement rates. Treumer and colleagues showed an average LogMAR BCVA improvement of -0.7 at 1 month follow up (n = 12), -0.9 at 3 months follow up (n = 41) and -0.8 at long term follow up (n = 26) using a combination of vitrectomy and gas tamponade with subretinal TPA and bevacizumab [12,27-30]. This compares well with Group 2 in the present study, which demonstrates an average BCVA improvement of -0.57 ($p = 0.004$), -0.89 ($p < 0.001$) and -0.80 ($p < 0.001$) at 1, 3 and 6 months follow up. In a more recent study, Gonzalez-Lopez and colleagues demonstrated an improvement of LogMAR BCVA of -0.59 ± 0.61 at one year follow up (n = 45) using the same combined treatment regimen utilised in 15 out of 19 patients included in Group 2 [18]. Although our comparatively smaller sample size demonstrated greater BCVA gains, SMH area was comparable in the Gonzalez-Lopez series and Group 2 (37.90mm^2 ± 16.63).

Although SMH thickness/height has been postulated to affect treatment outcome, it has yet be demonstrated to be a prognostic indicator [1,18]. SMH height measurement on Fourier Domain OCT is subject to error due to poor visualisation of the RPE or haemorrhage base, as discussed elsewhere [18]. We found that Spectral Domain OCT images were not subject to this problem. SMH height was estimated on Fourier Domain OCT images by varying contrast to identify the base of the haemorrhage in attempt to maintain accuracy. We demonstrate significant reductions in measured SMH height on OCT imaging, where no difference was observed between groups. Recently de Jong and Colleagues measured haemorrhage volume using spectral domain OCT, potentially allowing quantification of this process [20]. Next generation OCT imaging, including Swept Source, may offer more reliable means to standardise reporting of this SMH height to define its importance.

Pre-operative haemorrhage area has been described as a potential prognostic parameter [2,3]. We measured SMH area using OCT software as defined elsewhere, finding very significant reductions in average area in Group 2, with no difference found with Group 1 [18]. Herein we have not sought to analyse for prognostic factors this given the limited sample size in each group, making multivariate analysis unreliable.

Treatment with Intravitreal rTPA and gas have been associated with few complications but most frequently with vitreous haemorrhage (VH) as a result of breakthrough haemorrhage [31]. We observed one VH that occurred 3 months after treatment, which is similar to the 15% rate reported by Wu et al. using the same rTPA dose of 50mcg and confirms that VH does not occur frequently in nAMD treated with intravitreal rTPA [31-33]. We did not find a higher rate of surgical complications in those treated with vitrectomy. We report a complication rate of 10.52% with vitrectomy, which compares well to 26.83% (n = 41) and 48.9% (n = 45) reported in Treumer et al. and Gonzalez-Lopez et al. series [16,18].

Intravitreal treatment potentially affords a prompt treatment modality that may be performed outside of the operating theatre, effectively minimising the delay in treatment and averting the toxic effects of blood as postulated elsewhere [16,27]. While our series demonstrates significant BCVA gains with vitrectomy, there was no significant difference with intravitreal treatment. As previously reported, pre-vitrectomy intravitreal treatment may be an ideal solution to buy time to perform more definitive surgery in selected patients who are less likely to respond to intravitreal treatment alone [34,35]. However, it still remains unclear what treatment regimen should be the standard of care for SMH confined to the temporal arcade vessels. Our study supports de Jong and colleagues who found efficacy equivocal between intravitreal and subretinal treatment for SMH [20]. This is also in keeping with other recent comparative studies [21,22]. Until a RCT can be facilitated, it is difficult to postulate greater efficacy of one technique over the other. However, SMH as complication of nAMD does not occur frequently, which has posed difficulties in performing a randomised controlled trial in the past.

This study was limited by the sample size and retrospective collection of data. The lack of a control group also makes it difficult to draw conclusions. The differing timeframe for selection for treatment and differences post operative anti-VEGF regimes make interpretation of visual gains challenging. Insufficient data between the two centres for posterior vitreous detachment (PVD) status and pre- and post-operative intraocular pressures (IOP) was available to include in our analysis. While PVD is not often reported in SMH studies, it is useful for planning vitrectomy in the context of vitreomacular traction [10]. IOP has been reported in a number of studies as there has been concern of post-operative ocular hypertension following injection of a large volume [20,27,36]. Prophylactic and therapeutic anterior chamber paracentesis or medication have been reported to mitigate potential ischaemic episodes. However, IOP and PVD status has not been consistently reported in large case series to date. A prospective study would standardise this.

In conclusion, this study adds comparative data from two tertiary centres serving a similar population that shows similar efficacy for haemodisplacement and visual acuity gains, with similar safety profiles between intravitreal and vitrectomy assisted haemodisplacement techniques. This is in keeping with the latest studies comparing these techniques that conclude that neither technique shows a significant benefit over the other. Notwithstanding the limitations, our study is one of the largest in this field and adds to the understanding of the management of this condition. It also supports the use of either intravitreal or vitrectomy assisted haemodisplacement techniques as a first line treatment for SMH as a complication of nAMD.

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