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RESEARCH

Comparison of current treatment strategies for AMD-related submacular haemorrhage: Real-world outcomes

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Abstract

Purpose Comparison of available treatment modalities for neovascular AMD-related submacular haemorrhage including robot-assisted subretinal drug delivery.

Methods Single centre, long-term, retrospective analysis of patients treated for nAMD-related submacular haemorrhage. For each treatment group, outcomes assessed included haemorrhage resolution and best corrected visual acuity (BCVA) change with sub-analyses by haemorrhage size.

Results We identified 55 patients with classic nAMD-related submacular haemorrhage. We observed a preference for the surgical approach injecting subretinal TPA (manual or robotic) with intravitreal anti-VEGF and pneumatic displacement (30 cases: 8:10:12 ratio of small:medium:large haemorrhage), over intravitreal TPA/anti-VEGF/pneumatic displacement (13 cases: 4:5:4) or intravitreal anti-VEGF alone (12 cases 8:4:0). Subretinal TPA led to significant decrease in haemorrhage size by month 1 compared to intravitreal TPA or anti-VEGF monotherapy ($p < 0.0001$, Tukey test) with most cases resolving by 12 months irrespective of the treatment group. Mean BCVA change over 12 months was not significantly different between treatment groups, although by 12 months + 15 letter gain was observed post subretinal TPA, + 11 after intravitreal TPA and -7 letters loss after anti-VEGF monotherapy. A higher proportion of patients in the surgical group (53% subretinal and 69% intravitreal TPA) were associated with BCVA improvement, or stabilisation (33% and 15% respectively), while anti-VEGF alone led to more frequent BCVA deteriorations (50% of cases). Robot-assisted TPA injection showed comparable result to the manual technique.

Conclusions Subretinal TPA approach, manual and robotic, resulted most effective clearance of submacular haemorrhage in the early post-operative phase, with some potential clinical benefit for longer term visual function.

Key messages

What is known

- Acute submacular haemorrhage secondary to neovascular AMD is a vision threatening emergency, but optimal management guidelines remain uncertain.

What is new

- Subretinal TPA with vitrectomy and pneumatic displacement achieves significantly faster early haemorrhage clearance than intravitreal TPA or anti-VEGF monotherapy.
- In our centre, surgical displacement strategies are associated with a higher likelihood of clinically meaningful visual improvement at 12 months compared with anti-VEGF monotherapy.
- From our initial experience of robotic eye surgery, robot-assisted subretinal TPA delivery yields outcomes comparable to manual injection, supporting continued investigation of robotic drug delivery as a feasible clinical platform.

Keywords Age-related macular degeneration · Subretinal/intraocular drug delivery · Submacular haemorrhage · Robotic technologies in surgery

Extended author information available on the last page of the article

Introduction

Age-related macular degeneration (AMD) is a chronic, progressive, degenerative disease of the macula typically affecting people over the age of 50. Worldwide, it is the 4th most common cause of blindness in people above that age [1] with a prevalence of approximately 12%, projected to affect about 288 million people globally by 2040 [2, 3]. Neovascular AMD (nAMD), a late form of the disease, is classically caused by vascular endothelial growth factor (VEGF)-driven choroidal neovascularisation (CNV), and less commonly occurs due to polypoidal choroidal vasculopathy (PCV) or retinal angiomatous proliferation (RAP) [4]. The pathological CNV-related blood vessels are highly susceptible to leakage and haemorrhage [5]. Accumulation of blood between the neurosensory retina and the RPE within the macular region [6], a submacular haemorrhage, is a serious and highly vision-threatening complication of nAMD. This is due to the rapid toxic effect of blood on the retina, barrier to diffusion, and shearing of photoreceptors by fibrin clots leading to physical separation of photoreceptors from the retinal pigment epithelium [7]. Although the incidence is low, at 4.6 per 1000 patients per year [8] the natural progression of the disease is poor. If untreated, in 80% of cases, submacular haemorrhages lead to persistent loss of visual acuity ranging from 20/100 to light perception [9].

Submacular haemorrhage therefore represents an ophthalmological emergency requiring urgent intervention, however, no gold-standard guidelines for management exist to date. The range of available treatments is wide, including observation, medical treatment with regular anti-VEGF injections or surgical intervention [10]. Anti-VEGF injections are used to promote haemorrhage resolution and prevent future recurrence by reducing neovascular drive from CNV. The surgical interventions, usually done additionally to anti-VEGF therapy, involve pneumatic displacement aimed at removing the haemorrhage off the macula thus limiting its toxic effects. Concurrent administration of tissue plasminogen activator (TPA), either intravitreal or subretinal, helps the displacement by liquefying the clot [11].

Most available studies investigated the outcomes of only a single treatment or compared different surgical interventions. Very few studies have compared more than two methods, especially within a single ophthalmological centre. In our study, we looked at the anatomical and functional outcomes of anti-VEGF monotherapy and compared them to those achieved with additional surgical intervention, involving either vitrectomy, subretinal TPA injection and pneumatic displacement or intravitreal TPA injection with pneumatic displacement. We also looked at the same outcomes following the classic manual versus robot-assisted subretinal TPA injection to further investigate the potential use of robotic technologies in subretinal drug delivery.

Methods

Patients and groups

The study is a retrospective analysis (clinical trial number: not applicable) of patients identified from an inpatient database of a single tertiary treatment referral centre, the John Radcliffe Hospital, in Oxford between September 2014 and 2023 using the Medisoft Ophthalmology software. The programme was used to generate a list of patients with nAMD-related submacular haemorrhage. The inclusion criteria were patients with a classic nAMD-driven submacular haemorrhage measuring ≥ 1 disc diameter in greatest linear dimension and ≥ 125 µm thick at fovea, presenting less than 2 weeks from onset of symptoms making the patient eligible for all treatment options. As the natural history and response to treatment and prognosis may differ for non-classic nAMD cases, patients with haemorrhages believed to be due to RAP ($n=5$) or PCV ($n=3$) were excluded. The identified patients were divided into three groups based on treatment received. Anti-VEGF monotherapy group included patients treated with regular injections of 0.5 mg of ranibizumab, 1.25 mg of bevacizumab or 2 mg of aflibercept. The remaining two groups received additional surgical intervention at the beginning of treatment. The subretinal injection group was treated with standard 25-gauge 3-port pars plana vitrectomy (PPV), followed by intraoperative OCT-guided (Zeiss Resight 7000) subretinal injection of TPA (up to 100µL of 1 mg/ml solution) via a 41-gauge tip cannula, and air-fluid exchange. 13 cases were left in air (including the 6 robotic cases), 12 received SF_6 (sulphur hexafluoride) and 5 C_3F_8 (perfluoropropane). All patients in this group were instructed to posture face-down for 5–7 days postoperatively.

The intravitreal group received an intravitreal injection of TPA (30-gauge needle, 50 µL of 1 mg/mL solution) and C_3F_8 (30-gauge needle, 0.3–0.4 ml of 100% C_3F_8), followed by anterior chamber paracentesis immediately after gas injection to prevent acute spike in intraocular pressure. Patients were also asked to posture face-down for 5–7 days postoperatively.

Patients were further subdivided into three groups based on en face OCT haemorrhage size: small (≤ 5 disc diameters), medium (5–10 disc diameters), and large (≥ 10 disc diameters). Division by central foveal thickness was not conducted due to thick SMH preventing precise measurement in some cases and results of previous research indicating no significant correlation with final visual outcome [8, 12]. Maximum haemorrhage height at diagnosis was

measured for completeness. The measurements were performed on the central foveal OCT B-scan OCT, defined as the vertical distance from the retinal pigment epithelium (RPE) to the inner surface of the haemorrhage at the point of maximum height. Measurements were available in 49 of 55 patients (89%), as in 6 cases, haemorrhage volume precluded reliable identification of haemorrhage borders.

Additionally, for the patients who received subretinal TPA injection, the method of drug administration, whether robot-assisted, using the Preceyes Surgical System [13], or done manually by a trained surgeon, was recorded.

The collected data included age at diagnosis, time-to-presentation, gender, past ophthalmological history, complications and related interventions, number of anti-VEGF injections, best corrected visual acuity (BCVA), OCT and Optos widefield (Optos WF) retinal imaging.

Study outcomes

For this study, both the structural and functional outcomes of each treatment group were analysed. We first assessed treatment-induced haemorrhage resolution as per OCT images from Heyex (Heidelberg Engineering GmbH, Heidelberg, Germany) and the haemorrhage areas, both en face and cross-sectional at the fovea, were measured on diagnosis and at 3 follow-up timepoints (1 month, 3 months and 12 months). Additionally, Optos WF images were collected to support the measurements, and complete haemorrhage resolution was defined as disappearance of the haemorrhage on both cross-sectional and en face OCT imaging. Haemorrhage recurrence was defined as reappearance of submacular haemorrhage on OCT following documented complete resolution. We also looked at the effect of treatment on visual acuity over the 12-month follow up period. Available BCVA measurements (ETDRS letters) were collected at the earliest available pre-diagnosis, diagnosis, 1 month, 3 months and 12 months timepoints. For the assessment of visual outcomes, patients were categorised at 12 months as improved (≥10 ETDRS letter gain from diagnosis), stabilised (within 10 letters of diagnosis), or deteriorated (≥10 ETDRS letter loss from diagnosis).

Analysis and statistics

Data analysis and statistics were performed using the GraphPad Prism software (version 10.0.0) and R (version 4.2.1). To assess success rate of haemorrhage resolution, for each data set the number of complete resolutions by specific follow-up timepoint was identified and plotted on cumulative bar graphs.

For BCVA change analysis, firstly the mean results for each group analysed were plotted using line graphs. The mean value changes were used to investigate possible trends in BCVA over the 12-month period following initiation of treatment. Additionally, the proportion of cases where the BCVA has improved, stabilised, or deteriorated was calculated and plotted on a separate set of graphs. A threshold of 10 ETDRS letters was used to analyse the final effect of submacular haemorrhage on vision.

For statistical analysis normal distribution of the data was assessed using Shapiro–Wilk test ($p<0.05$). Two separate mixed effects models were fitted: one with BCVA as the outcome and one with OCT haemorrhage area as the outcome, with patient ID set as the random variable to account for the repeated measures design. Residuals were normally distributed and homoscedastic in the BCVA model. Accordingly, a linear mixed effects model with a Gaussian distribution function was fitted using the lme4 package [14]. Residuals were non-normally distributed and homoscedastic in the OCT changes model and so a robust linear mixed effects model was used to account for the influence of one outlier case [15–17]. Statistical difference was assessed using the Tukey test with values $p<0.05$ used as threshold for significance. To assess the robustness of the primary findings, two pre-specified sensitivity analyses were performed. Sensitivity Analysis 1 excluded patients with a large sub-RPE haemorrhage component ($n=7$; 2 anti-VEGF monotherapy, 3 subretinal TPA group, 2 intravitreal TPA group). Sensitivity Analysis 2 excluded patients with massive haemorrhage extending beyond the vascular arcades ($n=9$; 0 anti-VEGF monotherapy, 6 subretinal TPA group, 3 intravitreal TPA group).

Results

Participant demographics

Overall, 55 eyes of 55 patients with nAMD-related submacular haemorrhage were included in the study and split into groups according to treatment strategies (Fig. 1). Time-to-presentation (1–14 days) was not significantly different between the groups ($p>0.05$, Tukey test). The mean number of anti-VEGF injections over the 12-month follow-up period was 7 for the anti-VEGF monotherapy group, compared with 5 for both the surgical groups. Demographics and clinical data is presented in Table 1.

In our centre there was a preference for the surgical approach injecting subretinal TPA (manual or robotic) with intravitreal anti-VEGF and pneumatic displacement (30 cases: 8:10:12 ratio of small:medium:large haemorrhage), over intravitreal TPA/anti-VEGF/pneumatic displacement (13 cases: 4:5:4) or intravitreal anti-VEGF alone (12 cases 8:4:0). Maximum haemorrhage height at diagnosis

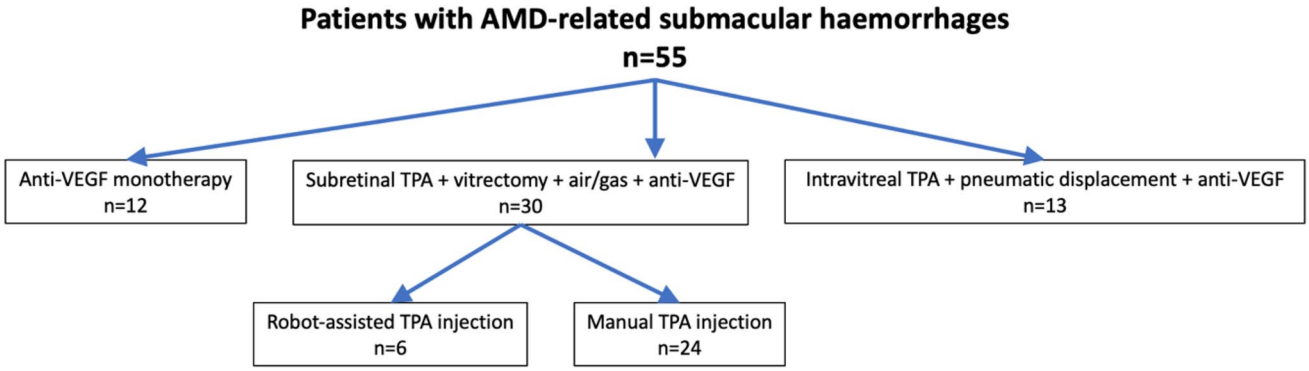

Fig. 1 Participants' flow chart showing the management groups with associated group numbers

Table 1 Demographics table for each treatment group. The top table shows the demographics of the main submacular haemorrhage treatment groups, anti-VEGF monotherapy, subretinal TPA and intravitreal TPA groups. The bottom table splits the subretinal TPA group based on method of drug administration (robot-assisted vs manual). For each table, information about the overall group size and size after stratification based on haemorrhage size ("small" ≤ 5 disc diameters, "medium" 5–10 disc diameters, "large" ≥ 10 disc diameters) is included. Additionally, data regarding time-to-presentation (days), gender, BCVA before and at diagnosis and number of anti-VEGF injections over the 12-month follow-up is provided

	No. of cases				Time-to-presentation [mean (range)]	Gender [M/F]	Age at diagnosis [M/F, total]	BCVA [ETDRS letters]		No. of injections [mean; 12 months]
	Total	≤5 DD	5–10 DD	≥10 DD				Pre-diagnosis	Diagnosis	
Anti-VEGF monotherapy	12	8	4	-	6 (1–12)	6/6	88/90, 89	62	44	7
Subretinal TPA	30	8	10	12	5 (1–14)	9/21	81/82, 82	65	18	5
Intravitreal TPA	13	4	5	4	6 (1–14)	9/4	81/83, 81	64	21	5
Overall	55	20	19	16	5 (1–14)	24/31	82/84, 83	63	24	6
	No. of cases				Time-to presentation [mean (range)]	Gender [M/F]	Age at diagnosis [M/F, total]	BCVA [ETDRS letters]		No. of injections [mean; 12 months]
	Total	≤5 DD	5–10 DD	≥10 DD				Pre-diagnosis	Diagnosis	
Robot-assisted TPA injection	6	1	2	3	5 (2–7)	2/4	73/77, 76	58	29	7
Manual TPA injection	24	7	8	9	5 (1–14)	7/17	84/83, 84	66	15	5

was measurable in 49 of 55 patients (89%), in 6 cases, haemorrhage volume precluded reliable identification of haemorrhage borders. Height increased with haemorrhage area, with median height of 262 µm for small, 352 µm for medium, and 716 µm for large haemorrhages; full descriptive statistics are presented in Supplementary Table 3. When stratified by the Manchester Protocol height threshold of 400 µm, 13 of 15 anti-VEGF monotherapy patients (87%) had haemorrhage height < 400 µm, compared with 5 of 22 subretinal TPA patients (23%) and 5 of 12 intravitreal TPA patients (42%). This distribution is consistent with height contributing to treatment allocation in a clinically coherent manner. Figure 2 shows representative retinal images from each treatment approach demonstrating a decrease in size of haemorrhage on both OCT and WF imaging in all presented cases. Further, more-detailed, analysis was therefore necessary to see if there were any differences between the treatment groups.

Effect of treatment on haemorrhage resolution

The effect of treatment on haemorrhage resolution was analysed by haemorrhage area measurements on cross-sectional OCT images (Heidelberg Engineering GmbH, Heidelberg, Germany) as shown on Fig. 3A.

The data for the proportion of cases with complete submacular haemorrhage resolutions in the entire patient cohort in shown in Fig. 3B. The surgical interventions, especially with subretinal TPA, led to earlier haemorrhage resolution compared to other groups. By 1 month of follow-up complete resolution of haemorrhage at the macula occurred in 26/30 (87%) of cases treated with subretinal TPA and 6/13 (46%) with intravitreal TPA, as compared to only 3/12 (25%) after anti-VEGF monotherapy. By the end of the 12-month follow-up, most cases (50/55 cases, 91%) resolved irrespective of the treatment type. Anti-VEGF monotherapy led to complete submacular haemorrhage resolution in 10/12 (83%)

patients. Additional surgical intervention induced resolution in 29/30 (97%) patients following subretinal TPA, and 11/13 (85%) patients treated with intravitreal TPA. Results of statistical analysis of haemorrhage size change throughout follow-up using the linear mixed effects model are shown in Appendix Fig. 2. The analysis demonstrated significant haemorrhage size reduction occurring at all follow-up timepoints with all treatment regimens ($p<0.05$, Tukey test). Comparison of the three treatment strategies showed significantly greater haemorrhage resolution between diagnosis and 1 month of follow-up after subretinal TPA treatment vs anti-VEGF monotherapy ($p<0.0001$, Tukey test) or intravitreal TPA ($p<0.0001$, Tukey test). There was no significant difference by 3 and 12-month follow-up timepoints ($p>0.05$, Tukey test).

Sensitivity analyses confirmed the robustness of these findings. After excluding cases with significant sub-RPE haemorrhage component (Sensitivity Analysis 1, $n=48$, 7 cases excluded), resolution rates and trends were consistent with the primary analysis, with no significant between-group differences at any timepoint ($p>0.05$, Tukey test). Exclusion of massive haemorrhage cases (Sensitivity Analysis 2, $n=46$, 9 cases excluded) preserved and notably strengthened the primary findings that subretinal TPA demonstrated significantly greater haemorrhage resolution compared with anti-VEGF monotherapy at 1 month ($p=0.001$, Tukey test) and 3 months ($p=0.006$, Tukey test), and intravitreal TPA vs anti-VEGF monotherapy at 1 month ($p=0.045$, Tukey test). Full results are presented in Supplementary Tables 1 and 2.

Within the subretinal TPA group, similar successful outcomes were achieved with both robot-assisted and manual methods of subretinal TPA injection at all points of the follow-up. By 12 months resolution occurred in 6/6 (100%) and 23/24 (96%) patients respectively with no statistical difference between the two methods at any point of the follow-up ($p>0.05$, Tukey test).

The entire patient cohort was divided into subgroups based on the size of the submacular haemorrhage at diagnosis. The results of this subanalysis are shown in Fig. 3C, D, and E. With regards to patient distribution, while the groups were similarly sized some clear trends were identified. In our centre the preference for surgical interventions with either subretinal TPA (manual or robotic) or intravitreal TPA over anti-VEGF monotherapy was especially noticeable with increasing haemorrhage size. As may have been expected, anti-VEGF monotherapy was primarily used in patients with small haemorrhages – in 8/12 (67%) patients treated with anti-VEGF injections only. For medium-sized haemorrhages ranging from 5–10-disc diameters, we saw a higher proportion of patients receiving additional surgical intervention, while for the large haemorrhages ≥ 10-disc diameters only the surgical interventions were used.

In all subgroups, at every follow-up timepoint, additional surgical interventions with TPA resulted in higher proportion of cases with resolved haemorrhages compared to anti-VEGF monotherapy. Subretinal and intravitreal TPA were both equally effective in patients with small haemorrhages, however, for medium- and large-sized haemorrhages subretinal TPA was more effective at all timepoints of the follow-up. Additionally, for large haemorrhages, only subretinal TPA was effective in inducing haemorrhage resolution by 1 month, occurring in 10/12 (83%) patients compared with 0/4 following intravitreal TPA.

Statistical analysis revealed a significant decrease in haemorrhage size over time for all treatment groups and haemorrhage size subgroups at all follow-up time points ($p<0.05$, Tukey test). However, there was no significant difference in outcomes between the treatment groups at any specified timepoint in the study for any haemorrhage size subgroup ($p>0.05$, Tukey test).

Effect of treatment on visual function

Figure 4 illustrates the mean BCVA [ETDRS letters] over the 12-month follow-up period. Additionally, the most recent BCVA before the onset of haemorrhage (pre-diagnosis) is included. The anti-VEGF monotherapy group showed better baseline mean BCVA than both surgical groups ($p<0.05$, Tukey test). Compared to BCVA on diagnosis, treatment with anti-VEGF monotherapy showed a mean 2-letter loss at 1 month ($p=0.344$, Tukey test), followed by a peak gain of 6 letters by 3 months ($p=0.0457$, Tukey test), and an overall loss of 7 letters by 12 months ($p=0.831$, Tukey test). Additional surgical intervention with subretinal TPA showed a peak mean 24-letter gain from baseline at 1 month ($p=0.0090$, Tukey test), a 23-letter gain by 3 months ($p=0.0214$, Tukey test) and an overall 15-letter gain at 12 months ($p=0.494$, Tukey test). Intravitreal TPA treatment group had a peak 16-letter gain at 1 month ($p=0.128$, Tukey test), levelling off at an 11-letter improvement by 12 months ($p=0.481$, Tukey test). There were no significant differences in BCVA outcomes between treatments at any timepoint ($p>0.05$, Tukey test).

Subanalysis by haemorrhage size (Appendix Fig. 1A-C) showed the following trends. For small haemorrhages surgical treatments appeared more effective compared to anti-VEGF monotherapy as both subretinal and intravitreal TPA led to mean BCVA improvement by 12 months (+17 and +21 letters respectively, $p>0.05$, Tukey test) whilst anti-VEGF treatment led to −10 letters loss ($p>0.05$, Tukey test). Treatment of medium-sized haemorrhages led to mean improvement in BCVA following anti-VEGF monotherapy (+2 letters, $p>0.05$, Tukey test) and both subretinal (+7 letters, $p>0.05$, Tukey test) and intravitreal TPA (+4 letters,

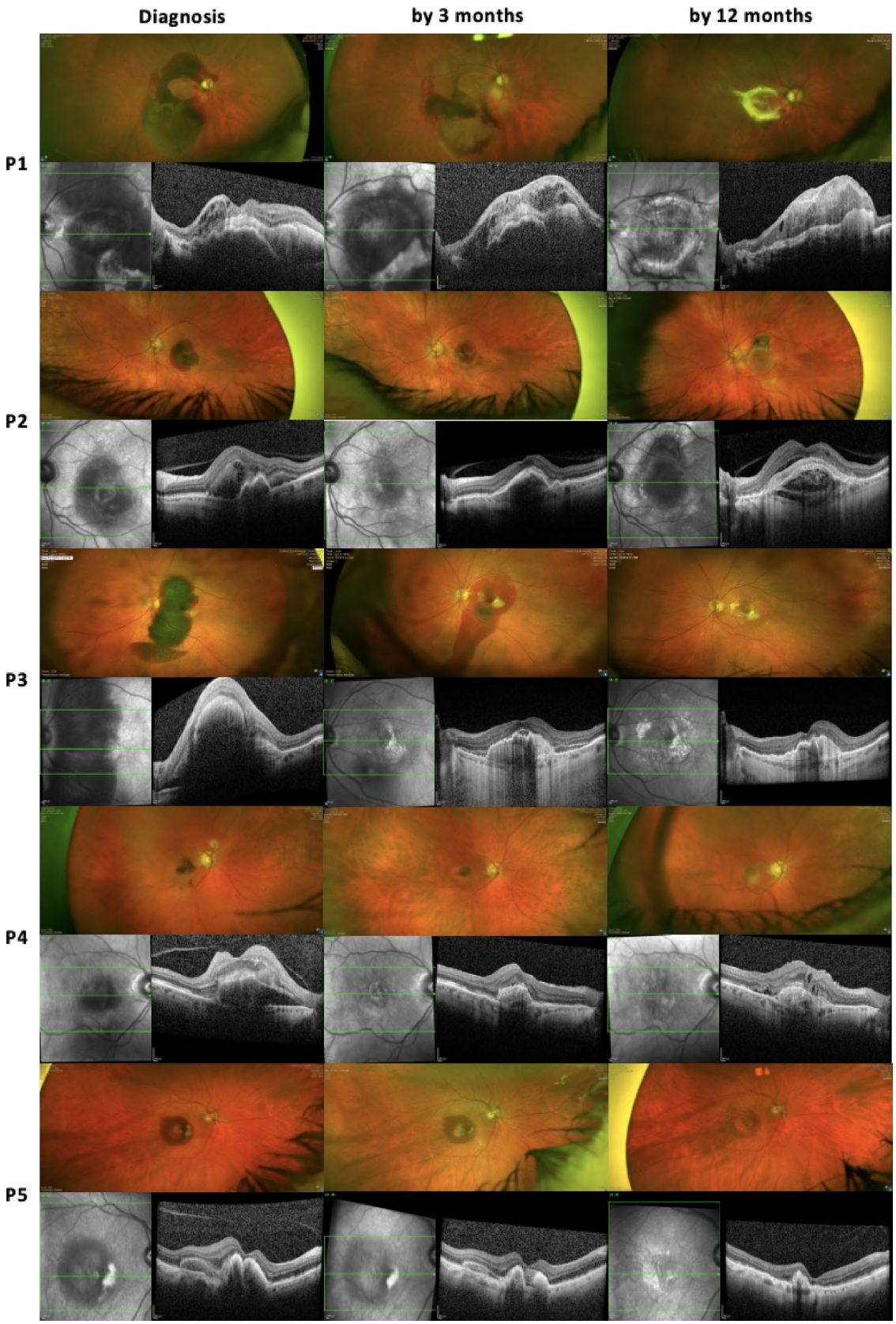
Diagnosis
by 3 months
by 12 months
P1
P2
P3
P4
P5

Fig. 2 Representative retinal images from our treatment approaches for nAMD-related submacular haemorrhage. OCT and Optos WF retinal images were taken for 5 patients (P1-P5) at diagnosis, by 3 months, and by 12 months, the endpoint of follow-up. P1 was managed conservatively. P2 received anti-VEGF monotherapy treatment. P3 from the subretinal TPA group was injected manually, while P4 was injected using a robot. P5 was managed with the intravitreal TPA protocol

$p > 0.05$ Tukey test). For large submacular haemorrhages we noted mean BCVA improvement with both subretinal TPA (+19 letters, $p > 0.05$, Tukey test) and intravitreal TPA (+9 letters, $p > 0.05$, Tukey test).

Comparison of robot-assisted vs. manual subretinal TPA injections (Appendix Fig. 1D) revealed similar BCVA recovery trends but with a mean improvement of 21 letters for manual injection ($n = 24$) ($p = 0.0050$, Tukey test) and 5 letters loss for robot-assisted delivery ($n = 6$) at 12 months ($p = 0.567$, Tukey test). However, no statistically significant differences were found between these methods at any follow-up timepoint ($p > 0.05$, Tukey test).

In addition to treatment effect on mean BCVA, we also looked at the proportion of patients whose vision improved, stabilised or deteriorated by 12 months compared to baseline. We assumed a threshold of 10 ETDRS letters to assess that, as shown in Fig. 5.

SEM) are shown for the entire patient cohort and different treatment groups.

In our study, out of 55 patients, 27 (49%) showed > 10 ETDRS letters improvement in BCVA, 16 (29%) stabilised within 10 ETDRS letters from baseline, and 12 (22%) cases experienced > 10 ETDRS letters loss at 12-month endpoint. Specifically, anti-VEGF monotherapy resulted in a higher proportion of deteriorations, in 6/12 patients (50%), compared to improvements in 2/12 (17%) or stabilisations in 4/12 (33%). In contrast, both intravitreal and subretinal TPA treatments were associated with more favourable outcomes; intravitreal TPA led to improvement in 9/13 (69%) of cases, stabilisation in 2/13 (15%) and deterioration in 2/13 (15%), while subretinal TPA resulted in improvement in 16/30 (53%), stabilisation in 10/30 (33%) and deterioration in 4/30 (13%) of cases. These trends were consistent across different sizes of submacular haemorrhage.

Visual outcome trends were preserved across both sensitivity analyses (Supplementary Tables 1 and 2), with surgical groups consistently achieving higher proportions of ≥ 10 ETDRS letter improvement at 12 months (subretinal TPA: 51.9–58.3%; intravitreal TPA: 70.0–72.7%) compared with anti-VEGF monotherapy (10.0–16.7%).

Adverse events

Adverse events were recorded for each group throughout the study. No intra-operative complications were reported irrespective of treatment group. Within the first month from treatment initiation, there were no reported complications after anti-VEGF monotherapy; there was one case of vitreous haemorrhage and one case of recurrent submacular haemorrhage in the subretinal TPA treatment group, and one case of persistent vitreous haemorrhage in the intravitreal TPA treatment group. By 12 months of follow-up, there were 12 reported cases of recurrent haemorrhage: 2/12 (17%) in the anti-VEGF monotherapy group (both at 6 months), 5/13 (17%) in the subretinal TPA group (1 at 2, 2 at 3 and 2 at 9 months) and 5/13 (38%) in the intravitreal TPA group (3 at 3 months, 1 at 6 months and 1 at 12 months). No patient was reported to have had a recurrence of submacular haemorrhage more than once. In each recurrence case, the same treatment was repeated within 2 weeks of diagnosis. Repeated subretinal TPA injections led to resolution in 4/5 eyes, while intravitreal TPA led to resolution in 3/5 eyes. In the two cases of haemorrhage recurrence in the anti-VEGF monotherapy group, continued treatment did not result in complete resolution by the end of the follow-up period.

Discussion

Our study compared current treatment strategies for AMD-related acute submacular haemorrhage in real-world clinical setting. Overall, our study favoured additional surgical intervention compared to anti-VEGF monotherapy. We find that the subretinal TPA surgical approach, both manual and robotic, resulted in the most effective displacement of submacular haemorrhage in the early post-operative phase, with trends towards more favourable visual outcomes at 12 months compared to the non-surgical anti-VEGF treatment.

The anti-VEGF monotherapy, nonetheless, also resulted in a high rate of submacular haemorrhage resolution. However, there was an overall loss in visual acuity at 12-month endpoint, as has been observed by other groups [18, 19]. This occurred despite better mean vision at diagnosis compared to other treatment groups, and with no cases returning to pre-diagnosis vision. Given that our patients receiving anti-VEGF monotherapy generally had better BCVA at diagnosis, than those undergoing surgical treatments, there might be a potential ceiling effect in visual recovery observed in our cohort. A recent meta-analysis of 11 studies on anti-VEGF injections for sub-macular haemorrhage (444 eyes) noted a modest loss of vision of −0.16 LogMAR (CI −0.24 to −0.08) in this group of patients compared to −0.36 LogMAR loss for surgical group (12 studies, 195 eyes) with no significant difference [20]. There was however a high heterogeneity in surgical studies making direct comparisons difficult.

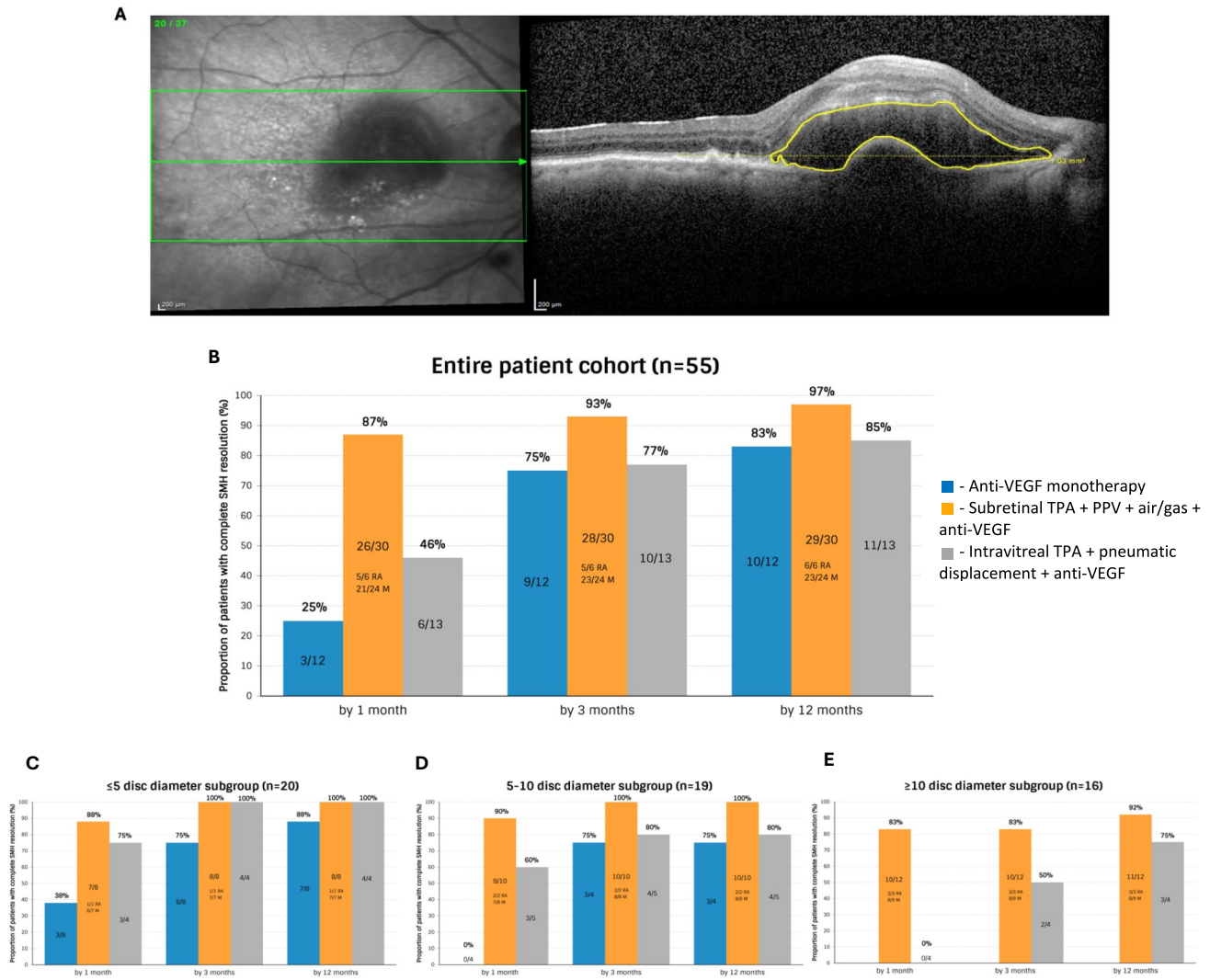

Fig. 3 Effect of treatment on submacular haemorrhage resolution. An example of submacular haemorrhage shown on a cross-sectional OCT image and highlighted in yellow (**A**). The proportion of patients with complete submacular haemorrhage resolution for the entire patient cohort (**B**) and the subgroups based on submacular haemorrhage size: ≤5 (**C**), 5–10 (**D**) and ≥10-disc diameter (**E**). The proportion of patients with resolved haemorrhage is included above each bar with a cumulative number of cases per respective group annotated in the middle of each bar. For subretinal TPA group, proportion of resolved cases following robot-assisted (RA) and manual (M) injection is included

Irrespective of the treatment arm, this lack of BCVA improvement at 12 months, despite successful haemorrhage clearance, might be due to the rapid, irreversible toxic effect of blood on the retina. The irreversible retinal damage including photoreceptor destruction, shown to occur from around 3 days post haemorrhage onset, might result in final poor visual outcome. In the long term, the damage to the retina and RPE has been shown to lead to irreversible fibrosis and atrophy [21]. The TAPAS trial reported a trend toward reduced fibrosis at 12 months in TPA-treated eyes compared to those that did not receive TPA, suggesting that early clot dissolution may mitigate some of this long-term retinal damage [22].

Importantly, our study as well as other reports [23–25] show that most haemorrhage resolutions occurred earlier with interventional groups (87% cases resolved by month 1) compared to anti-VEGF monotherapy (25% cases resolved), irrespective of baseline haemorrage size. This faster visual recovery means that patients regain useful vision sooner, even if final visual acuity at 12 months is similar. For an elderly AMD patient, recovering reading vision or mobility weeks to months earlier can have substantial quality-of-life benefits, reducing falls and injuries, dependence on carers and improving functional status. Thus, although accelerated clearance of submacular haemorrhage may not necessarily translate into superior final visual acuity, it may provide important clinical

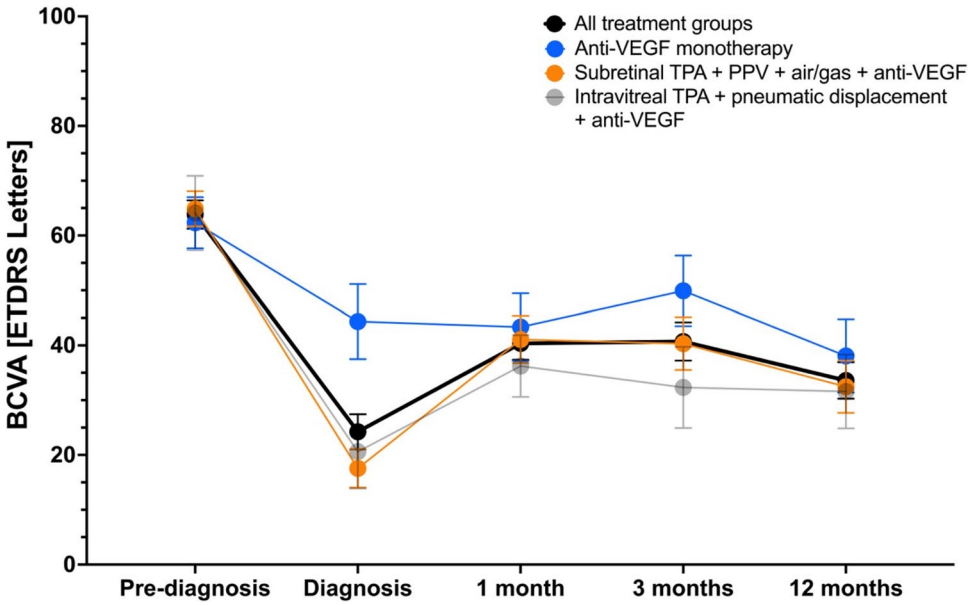

Fig. 4 Effect of submacular haemorrhage treatment on visual function. Mean best corrected visual acuity (BCVA) in ETDRS letters over 12-month follow-up period is recorded. Results (mean BCVA±)

benefits through earlier restoration of useful vision, reduction in the duration of severe visual impairment, improved visual function and quality of life, and earlier visualisation and treatment of the underlying neovascular lesion. These patient-centred benefits may not be adequately captured by conventional visual acuity endpoints alone. Notably, the mean number of anti-VEGF injections over the 12-month follow-up was lower in both surgical groups compare with anti-VEGF monotherapy groups, suggesting that surgical haemorrhage displacement may reduce subsequent anti-VEGF burden, potentially by facilitating access of anti-VEGF agents to the underlying CNV following blood clearance.

The results of our study also favoured subretinal over intravitreal TPA approach. By 1 month of follow-up complete resolution of haemorrhage at the macula occurred in 87% of cases treated with subretinal TPA compared to 46% with intravitreal TPA regardless of haemorrhage size. Subretinal and intravitreal TPA were both equally effective in patients with small haemorrhages, however, for medium- and large-sized haemorrhages subretinal TPA was more effective at all timepoints of the follow-up. Additionally, for large haemorrhages, only subretinal TPA was effective in inducing haemorrhage resolution by 1 month, occurring in 10/12 (83%) patients compared with 0/4 following intravitreal TPA. Notably, in our study we recorded a high recurrence rate of submacular haemorrhage following intravitreal TPA treatment, occurring in 5 of 13 cases (38%), all needing further intervention. The high rate of haemorrhage recurrence with intravitreal TPA, as compared to other treatment approaches, has been reported previously and could be an additional factor affecting final visual outcomes in this treatment group [26]. The literature currently remains divided regarding the superiority of either approach. The potential benefit of subretinal TPA is its delivery directly at the site of the clot, dispersing and dissolving the blood to be further displaced away from the fovea by pneumatic tamponade [27, 28]. Additionally, studies on animal models suggest that intravitreal TPA has limited diffusion across the neurosensory retina, which may reduce its effectiveness in displacing haemorrhage from the fovea [29]. Some clinical studies have reported superior improvement in BCVA following subretinal vs intravitreal TPA treatment [30, 31] whereas others showed no statistically significant difference in outcomes between the two treatments [32]. A randomised superiority STAR study [25], directly compared vitrectomy with subretinal TPA and gas, versus intravitreal TPA and gas in 90 patients with larger bleeds (>2 optic disc areas) and did not prove superior visual gains for vitrectomy with subretinal TPA at 3 months. Both groups showed similar improvements in acuity by 16 letters with majority of improvement occurring by 1 month and then stabilising by month 6. Interestingly, a factorial randomised clinical trial, the TAPAS trial, suggests that TPA alone, with or without the gas, increases the chance of visual gain when added to ranibizumab therapy for neovascular AMD in eyes with submacular haemorrhage, warranting consideration of additional clinical trials [22]. The combination of subretinal TPA with concurrent subretinal anti-VEGF delivery has also been explored in the context of PPV. The Native and Submarine studies demonstrated comparable visual and anatomical outcomes across different anti-VEGF agents delivered subretinally, with the Native study additionally reporting significantly reduced need for subsequent anti-VEGF injections when aflibercept was delivered subretinally compared to intravitreal application, suggesting a potential benefit of subretinal anti-VEGF delivery on long-term CNV management [33, 34].

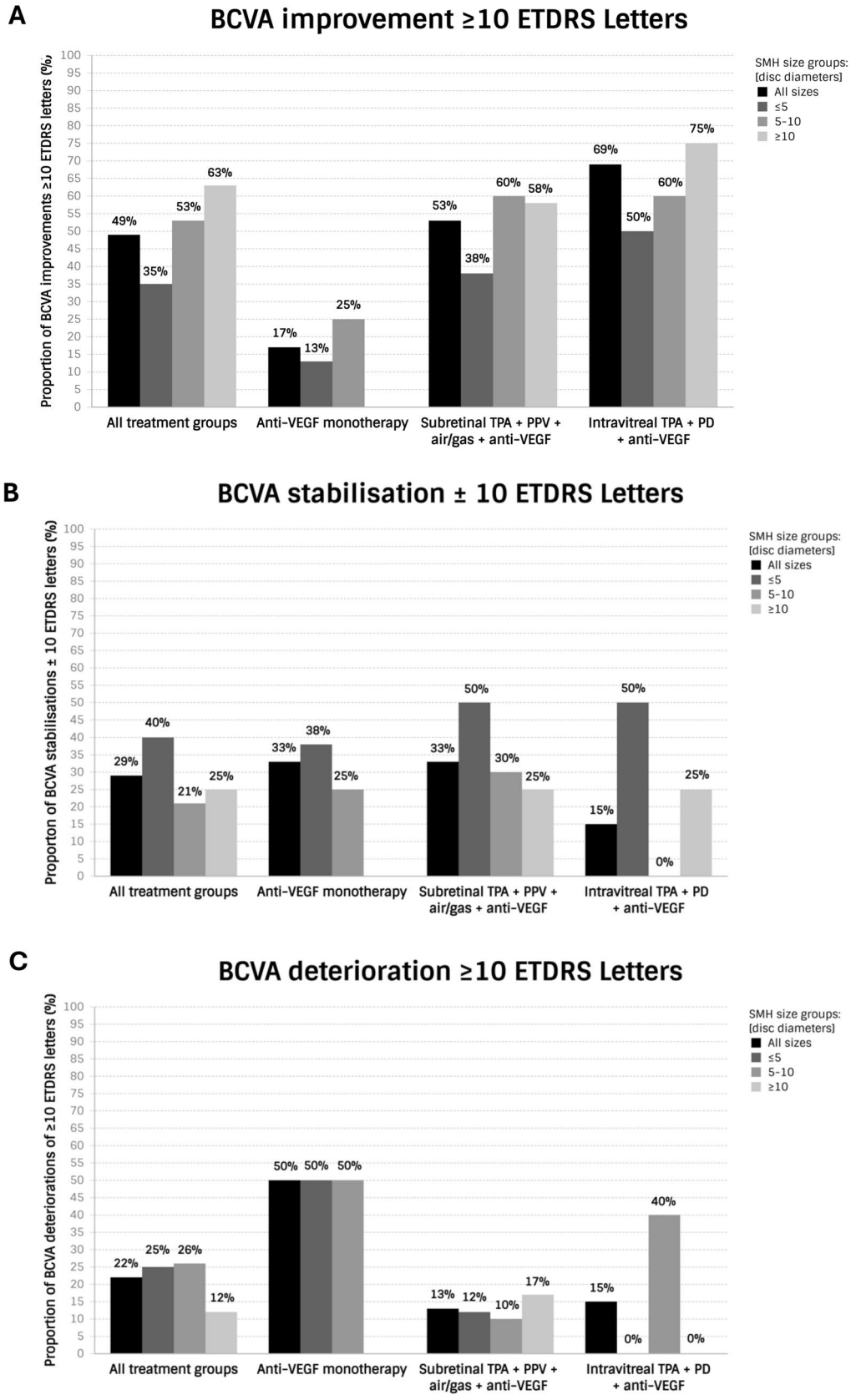
A
BCVA improvement ≥10 ETDRS Letters
Proportion of BCVA improvements ≥10 ETDRS letters (%)
SMH size groups: [disc diameters]
All sizes
≤5
5-10
≥10
49%
35%
53%
63%
17%
13%
25%
53%
38%
60%
58%
69%
50%
60%
75%
All treatment groups
Anti-VEGF monotherapy
Subretinal TPA + PPV + air/gas + anti-VEGF
Intravitreal TPA + PD + anti-VEGF
B
BCVA stabilisation ± 10 ETDRS Letters
Proporton of BCVA stabilisations ± 10 ETDRS letters (%)
SMH size groups: [disc diameters]
All sizes
≤5
5-10
≥10
29%
40%
21%
25%
33%
38%
25%
33%
50%
30%
25%
15%
50%
0%
25%
All treatment groups
Anti-VEGF monotherapy
Subretinal TPA + PPV + air/gas + anti-VEGF
Intravitreal TPA + PD + anti-VEGF
C
BCVA deterioration ≥10 ETDRS Letters
Proportion of BCVA deteriorations of ≥10 ETDRS letters (%)
SMH size groups: [disc diameters]
All sizes
≤5
5-10
≥10
22%
25%
26%
12%
50%
50%
50%
13%
12%
10%
17%
15%
0%
40%
0%
All treatment groups
Anti-VEGF monotherapy
Subretinal TPA + PPV + air/gas + anti-VEGF
Intravitreal TPA + PD + anti-VEGF

Fig. 5 Effect of submacular haemorrhage treatment on visual function in terms of proportion of patients with 10-letter BCVA change at 12 months compared to baseline. (**A**) Proportion of patients with BCVA improvement of≥10 ETDRS letters. (**B**) Proportion of patients with BCVA stabilisation within 10 ETDRS letters from baseline. (**C**) Proportion of patients with BCVA deterioration of≥10 ETDRS letters. As per legend, the data comprises of all treatment group segments including all submacular haemorrhage sizes and three subgroups for size-dependent analysis (≤5, 5–10, and≥10-disc diameter). Above each bar a percentage value for the respective proportion is included

Earlier studies in the field suggested correlation between duration, size (area), and central macular thickness of the baseline haemorrhage and visual recovery [9, 35]. The results of our study are more in line with recent research which suggest that neither size nor thickness of haemorrhage affect the final visual outcome [8, 12]. The haemorrhage-size subanalysis of our data however showed increased use of additional surgical interventions with increasing submacular haemorrhage size. As seen in other studies [18, 36], herein we show that for all haemorrhage sizes, surgical interventions particularly with subretinal TPA, outperformed the medical treatment with anti-VEGF monotherapy for induction of haemorrhage resolution although no clear size-effect correlation was noted with regards to the final visual outcome. A similar treatment preference was observed when maximal haemorrhage height was considered, with increasing reliance on surgical intervention as haemorrhage height increased. Of patients with haemorrhage heights<400 μm, 87% were managed with anti-VEGF monotherapy, while the majority of patients treated with subretinal TPA (77%) or intravitreal TPA (58%) had haemorrhage heights>400 μm. This is consistent with the Manchester Protocol, which recommends surgical intervention for haemorrhage heights over 400 μm [37]. While haemorrhage resolution rates by 12 months were high across all groups, baseline haemorrhage size remains an unclear predictor of final BCVA change at 12 months. Additionally, in our cohort, time-to-presentation was not significantly different between treatment groups, suggesting that the allocation into a treatment group was not influenced by presentation timing nor did it contribute to the differential outcomes observed. This supports the interpretation that the differences between groups in our study reflect treatment effect rather than baseline prognostic differences.

Robotic technologies offer a potential solution to the current human limits of manual dexterity. Within vitreoretinal ophthalmology, one possible application involves subretinal delivery of drugs such as TPA or gene therapy agents [38]. Our first in human clinical trial demonstrated feasibility and safety of robot-assisted subretinal TPA delivery in patients suffering from AMD-related submacular haemorrhage [13]. Here we note similar outcomes following robot-assisted vs manual TPA injection in terms of haemorrhage resolution and visual function up to 12 months follow-up, with no increased occurrence of adverse effects, most importantly haemorrhage recurrence. This correlates with the results of a recent systematic review that robot-assisted TPA injection is at least as effective and safe as the manual method [39]. Beyond robotic assistance, emerging devices such as the nano-vitreoretinal gateway are exploring vitrectomy-sparing approaches to subretinal injection, potentially reducing surgical complexity and associated complications [40]. A proposed pharmacokinetic advantage of avoiding vitrectomy is the extension of intravitreal anti-VEGF half-life, as vitrectomy is known to accelerate clearance of intravitreally administered anti-VEGF [41]. However, clinical experience with vitrectomy-free subretinal TPA delivery for submacular haemorrhage remains limited, and further studies are needed to determine whether the reduced surgical burden translates into equivalent haemorrhage displacement and visual outcomes. Continued research focused on optimising current microprecision robotic systems and integrating them into clinical practice could enhance the effectiveness, safety, and accessibility of these procedures, offering new options for the surgical management of eye diseases.

The main limitation of our study is its retrospective, non-randomised nature, and potential treatment selection bias occurring due to lack of established treatment guidelines making selection of the management strategy doctor- and patient-dependent rather than evidence-based. This limitation is shared across the field, as a recent comprehensive review noted, no universally accepted treatment algorithm currently exists for AMD-related submacular haemorrhage [42]. Our cohort also included patients with significant sub-RPE haemorrhage component ($n=7$) and massive haemorrhage extending beyond the vascular arcades ($n=9$), subgroups which carry different natural histories and prognoses. These cases were retained in the primary analysis to reflect real-world clinical practice. Notably, all 9 massive haemorrhage cases were managed surgically (6 subretinal TPA, 3 intravitreal TPA), with none allocated to anti-VEGF monotherapy alone, which is consistent with clinical judgement that larger haemorrhages warrant more aggressive intervention. This further illustrates the inherent treatment selection bias of a retrospective series. However, sensitivity analyses excluding these subgroups confirmed that the primary findings are preserved and, in the case of massive haemorrhage exclusion, strengthened. The baseline imbalance between the studied groups warrants further acknowledgment. Anti-VEGF monotherapy patients had a higher mean BCVA compared with subretinal and intravitreal TPA groups, as well as smaller haemorrhage burden across both dimensioned analysed in this study. This means that surgical groups were managing a substantially more severe case mix at baseline, such that any visual benefit observed in the surgical arms should be interpreted as a conservative estimate of the true treatment effect. Definitive comparative

efficacy data requires a prospective randomised design, our real-world data are intended to characterise current practice and inform hypothesis generation for such trials.

The ongoing prospective randomised controlled TIGER study [43] will hopefully provide some definitive answers, and so the results of this trial are awaited in anticipation. Given the rarity of the condition, our study nonetheless represents one of the largest single-centre studies on the topic to date, with conclusions that can be used to guide future prospective research including variations on surgical protocols [37] and novel therapies on the horizon.

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