Outcomes of Surgical Treatment in Cases with Submacular Hemorrhage

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ABSTRACT

Purpose: The aim of this study was to evaluate the different surgical treatment techniques performed for patients with submacular hemorrhage (SMH) secondary to various etiologies in our clinic regarding anatomical and functional outcomes, and complications.

Materials and Method: We retrospectively evaluated patients who presented to our retina department and underwent surgical treatment with diagnosis of SMH between 2014 and 2017. In all patients included, the SMH etiologies, measurements of SMH thickness and area, duration and types of treatment modalities and complications were noted. Pre-and-postoperative best-corrected visual acuity (BCVA) and central macular thickness (CMT) values were also recorded.

Results: Overall, 54 eyes of 53 patients were included. The mean age was 69.4±13.0 (13-93) years while mean follow-up duration was 5.8±10.5 (3-43) months. The most common etiology was neovascular age-related macular degeneration (55.6%); followed by polypoidal choroidal vasculopathy (22.2%). It was noted that the mean BCVA was 2.0±0.8 (0.3-3) logMAR while the mean SMH thickness was 662.5±330.0 (197-1615) µm and the mean SMH area was 31.5±26.5 (2.8-145.3) mm^2 at presentation. A significant improvement was found in mean BCVA (0.28 logMAR) at the final visit ($p=0.041$). No significant relationship was found between BCVA improvement and SMH thickness or area at presentation ($p>0.05$)($r=-0.181$). The mean time from symptom onset to SMH treatment was 13.7±16.3 (1-95) days. There was a negative correlation between the time from symptom onset to SMH treatment and BCVA improvement ($p<0.001$)($r=-0.548$). There was a significant difference between CMT values at baseline and those on months 1, 3, 6, 12 and at final visit ($p<0.05$).

Conclusion: The different surgical approaches employed in cases with SMH due to various etiologies can provide significant improvement in visual prognosis. The time from symptom onset to SMH treatment is a significant predictor for the final visual acuity achieved by treatment.

Key words: Submacular hemorrhage, Etiology, surgery, Pars plana vitrectomy, Subretinal t-PA injection.

INTRODUCTION

The submacular hemorrhage (SMH) is one of the complications that may lead severe loss of vision, particularly in patients with advanced ages, and is often caused by choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD). Besides, the SMH development can be seen as a result of several abnormalities including retinal arteriolar macro-aneurysm (RAM), trauma, valsalva retinopathy, diabetic retinopathy, potential ocular histoplasmosis, myopic CNV, angioid cracks, intraocular tumors and some surgical interventions where postoperative bleeding occurs as a complications such as scleral buckling.[1,2] The damage caused by submacular hemorrhage results from toxicity due to accumulation of fibrin, iron and hemosiderin as well as clot retraction leading stress formation photoreceptor outer segments.[2] Besides, the direct mechanical barrier effect of SMH that hampers metabolic exchange between retinal pigment epithelium (RPE) and outer retina and atrophy and discoid scar formation due to its natural course are among mechanisms underlying damage.

The natural course of submacular hemorrhage is characterized by progressive loss of vision that varies duration of SMH, underlying disease and macular functionality before onset of hemorrhage. Particularly, SMH developed in presence of AMD and/or massive SMHs results in severe loss of vision.[3]

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Currently, intravitreal anti-VGEF (vascular endothelial growth factor) injection and gas/t-PA injection are preferred in the treatment of small SMHs while vitrectomy plus intravitreal/subretinal t-PA injection and pneumatic retinopexy procedures are preferred in larger and thick SMHs. Massive SMHs may require subretinal surgical intervention.[4-7] However, there is no consensus on standard approach to SMH treatment.

The aim of our study was to evaluate the different surgical treatment techniques performed for patients with submacular hemorrhage (SMH) secondary to various etiologies in our clinic regarding anatomical and functional outcomes, and complication.

MATERIAL AND METHOD

Patient Selection and Patient Groups

This retrospective study included patients who presented to Retina Unit of Beyoğlu Ophthalmology Application and Research Center, Health Sciences University and underwent surgical treatment with diagnosis of SMH due to various etiologies between January, 2014 and December, 2017. The patients with other ocular diseases that may cause loss of vision (corneal pathologies etc.), those unable to adhere postoperative position recommended and those with follow-up less than 3 months were excluded.

In all patients, data regarding age, gender, involved eye, ocular disorders, previous history of intraocular surgery, history of systemic diseases, anterior segment findings as assessed by slit lamp examination and fundus findings as assessed by indirect imaging were extracted. In addition, SMH etiology, time from onset of SMH to treatment, therapeutic approaches, type of intraocular gas if used, postoperative positions prescribed and follow-up duration were recorded. The etiological diagnosis was confirmed by findings of ophthalmoscopy, OCT (HRT, Hiedelberg Engineering, Heidelberg, Germany) fundus fluorescein angiography and, if needed, indocyanine green angiography.

The best-corrected visual acuity (BCVA) as assessed by Snellen charts at baseline and on months 1, 3, 6 and 12 and at final visit, IOP measurements by Goldmann applanation tonometry and central macular thickness as measured by SD-OCT were recorded. Preoperative thickness of subfoveal hemorrhage on preoperative OCT images and measurements of hemorrhage area and hemorrhage localizations on preoperative red-free fundus images were also recorded. As the quality of images were affected by media opacity during measurements, the OCT section providing most accurate measurement was selected. During SMH measurement, the distance between upper surface of SMH and inner surface of RPE was manually measured and recorded as central foveal thickness of SMH. Again, when assessing SD-OCT, we also recorded presence of PED, type of localization, maximum height and diameter measurements in involved eye. and choroidal thickness in contralateral eye. The type and number of preoperative and postoperative intravitreal injections were noted separately. The perioperative and postoperative complications, type of intervention and time from first intervention if re-intervention was needed and time from first intervention to cataract surgery if needed were also recorded.

Treatment Techniques

All surgical interventions were performed under local and general anesthesia. Following sterilization procedures, standard three-port 23 Gauge pars plana vitrectomy (Alcon Constellation®; Alcon Laboratories, Fort Worth, TX, USA) was performed. After core vitrectomy, posterior hyaloid membrane peeling was performed if not detached. If subretinal t-PA was planned, recombinant t-PA (Actilyse, Boehringer Ingelheim, Germany; dose, 12.5-25 µg/ 0.1 mL; maximum total dose, 100 µg) was injected to subretinal space using 41 G flexible micro-cannula. The t-PA injections were repeated if needed, ensuring sufficient retinal detachment in order to replace hemorrhage. If intravitreal t-PA was planned, recombinant t-PA (0.2 mL, 50 µg) was injected via intravitreal route. In cases in which hemorrhage drainage was preferred, the incision was extended after 5-10 minutes following subretinal t-PA injection in order to ensure drainage of liquefied hemorrhage.

If intraocular tamponade was used based of surgeon's preference, gas tamponade using 20% SF_6 or 14% C_3F_8 and patient positioning were performed. The patient was recommended to maintain postoperative position given.

In cases with smaller hemorrhage where no vitrectomy was performed, pneumatic retinopexy was preferred. Firstly, anterior chamber paracentesis was performed using 30 G needle to prevent elevation of intraocular pressure by drainage of 0.2 mL humor aqueous; following paracentesis, 02-0.5 mL pure SF_6 or C_3F_8 gas was injected to intravitreal distance using 30 G syringe via inferotemporal approach. The patient was placed to prone position in order to allow gas tamponade to remove from central macula. Intravitreal t-PA injection was performed in combination with pneumatic retinopexy, as described above, in some cases.

Based on surgeon's preference, anti-VGEF injection was performed without or after vitrectomy in some cases with SMH.

Anti-VGEF treatment was maintained in cases with finding of activation at postoperative period.

Statistical Analysis

All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences version 20.0.0; SPSS Inc., Chicago, IL, USA). For statistical purposes, the BCVA values were transformed into logMAR values (Logarithm of the Minimum Angle of Resolution).

The normal distribution of variables was assessed using Kolmogorov-Smirnov test. The Paired samples t test was used to compared dependent groups with normal distribution (parametric) while the Wilcoxon test was used to compare dependent groups with skewed distribution (non-parametric). A p value<0.05 was considered as statistically significant.

Pearson's correlation analysis was used to assess relationships between independent and dependent variables with normal distribution. A p value<0.05 was considered as statistically significant.

FINDINGS

In the study, we assessed 54 eyes of 53 patients with SMH including 34 men (64.2%) and 19 women (35.9%). Mean follow-up duration was 15.8±10.5 months (3-43 months). Table 1 summarizes demographic and clinical characteristics of the patients.

Table 1: *Demographic and clinical characteristics at presentation.*

Characteristics	Descriptions	Values
Patient/eye	n	53/54
Age (years)	Mean.± SD (min-max)	69,4 ± 13,0 (13 - 93)
Gender: **Male** **Female**	n(%)	 34 (%64,2) 19 (%35,9)
Eye: **Right** **Left**	n(%)	 26 (%48,1) 28 (%51,9)
Lens: **Phakic** **Pseudophakic** **Aphakic**	n(%)	 31 (%57,4) 22 (%40,7) 1 (%1,9)
Tonometry (mmHg)	Mean.± SD (min-max)	13,9 ± 3,1 (8 – 22)
Comorbid ocular disorder: **Cataract** **Glaucoma** **DRP** **Uveitis**	n(%)	 14 (%25,9) 2 (%3,7) 2 (%3,7) 1 (%1,9)
BCVA (logMAR)	Mean.± SD (min-max)	2,0 ± 0,8 (0,3 – 3)
CRT (µm)	Mean± SD (min-max)	932,3 ± 289,6 (491 – 1643)
PED: **Serous** **Hemorrhagic** **Fibrovascular**	n(%)	 3 (%5,6) 12 (%22,2) 7 (%13,0)
PED localization: **Subfoveal** **Extra-foveal**	n(%)	 12 (%22,2) 10 (%18,5)
PED Height (maximum)	Mean.± SD (min-max)	506,9 ± 160,8 (195 – 868) µm
PED Diameter (maximum)	Mean.± SD (min-max)	2056,5 ± 836,9 (915 – 4001) µm

DRP: Diabetic retinopathy, BCVA: best-corrected visual acuity, CRT: central retinal thickness, PED: Pigmentary epithelium detachment

When etiological distribution was assessed, it was found that the neovascular AMD was the most common etiology in 30 cases (55.6%); followed by the PCV in 12 cases (22.2%), macro-aneurysm in 6 cases (11.1%), trauma in 2 cases (3.7%), myopic CNVM in 2 cases (3.7%), RAP in one case (1.9%) and postoperative complication of previous surgery in one case (1.9%). It was observed that SMH as postoperative complication was developed following band cerclage surgery (Figure 1).

It was found that mean SMH thickness was 662.5 ± 330.0 (197 - 1615) µm while mean SMH area was 31.5 ± 26.5 (2.8 - 145.3) mm^2. No significant correlation was detected between visual acuity gain and SMH thickness or area at presentation ($p>0.05$) ($r=-0.181$). The mean time from symptom onset to SMH treatment was calculated as 13.7±16.3 (1-95) days. A negative correlation was detected between the time from symptom onset to SMH treatment and visual acuity gain ($p<0.001$)($r=-0.548$).

It was observed that 15 cases received intravitreal anti-VGEF treatment before SMH development and treatment.

The different treatment modalities were preferred by different surgeons in cases retrospectively included to the study. The most commonly preferred treatment modality was PPV in combination subretinal t-PA injection plus intraocular gas tamponade in 21 cases (38.9%); followed by addition of anti-VGEF injection to above-mentioned treatment in 14 cases (25.9%), PPV plus subretinal t-PA injection without tamponade in 10 cases (18.5%), intravitreal gas plus t-PA injection in 4 cases (7.4%), PPV plus subretinal t-PA with subsequent drainage procedure in 3 cases (5.6%) and intravitreal gas plus intravitreal anti-VGEF injection in 2 cases (3.7%). In cases underwent gas tamponade, it was seen that C_3F_8 was preferred in 21 cases (38.9% whereas SF_6 in 20 cases (37.0). The recombinant t-PA injection was performed via subretinal route in 46 cases (85.2%) and intravitreal route in 3 cases (5.6%). The patient positioning was documented as prone position in 36 cases (66.7%), erected position in 12 cases (16.7%), right lateral decubitus in 4 cases (7.4%) and left lateral decubitus in 2 cases (3.7%).

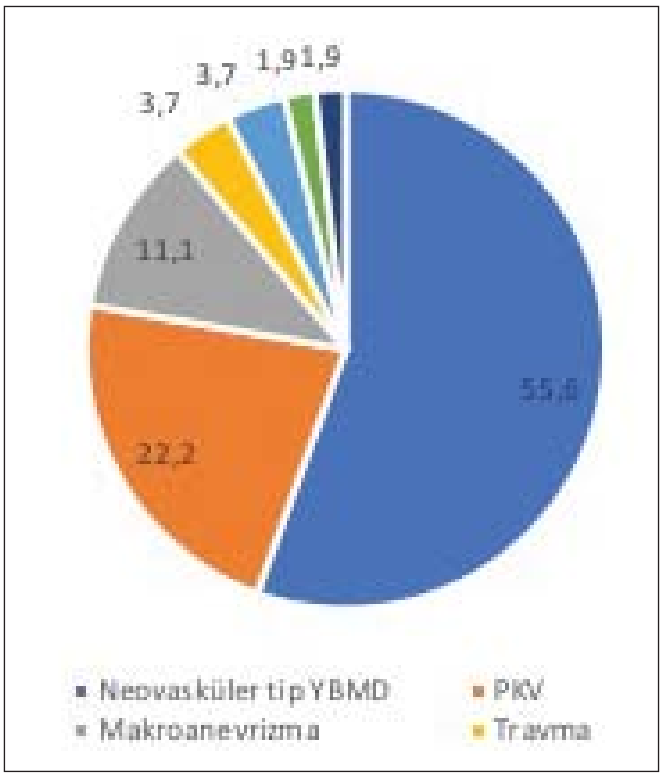

Figure 1: *Etiological distribution of SMH cases (%). (n=54).*

No preoperative complication was observed while temporary intraocular pressure elevation controlled with topical treatment (n=2; 3.7%), macular hole (n=2; 3.7%), IVH (n=3; 5.6%), RD (n=6; 11.1%) and endophthalmitis (n=1; 1.9%) were developed during postoperative follow-up period. Recurrent SMH was observed in 4 cases (7.4%). Of the 6 cases with RD, 3 cases (5.6%) were developed on postoperative week 1 whereas remaining 3 cases (5.6%) were developed between postoperative week 6 and 12. Of 3 cases with IVH, one case (1.9%) was developed on postoperative week 1 whereas remaining 2 cases (3.7%) were developed between postoperative week 6 and 12.

It was observed that re-operation was required in 14 cases (25.9%). Of these, re-operation was performed due to RD in 6 cases (11.1%), IVH in 3 cases (5.6%) and macular hole in 2 cases (3.7%) while 4 cases (7.4%) was re-operated due to recurrent SMH. Mean time from first to second surgeries was 68.9±70.0 days (3-270 days). During follow-up, phacoemulsification surgery was performed due to cataract development in 9 cases (16.7%).

It was found that mean BCVA was 1.67 ± 0.87 (0.22 - 3) logMAR on postoperative month 1, 1.65 ± 0.79 (0.40 - 3) logMAR on month 3, 1.76 ± 0.88 (0.22 - 3) logMAR on month 6, 1.71 ± 0.85 (0.30 - 3) logMAR at year 1 and 1.76 ± 0.81 (0.22 - 3) logMAR at final visit. Regarding visual acuity gain, it was found that there was significant increase in visual acuity on month 1 and 3 when compared to baseline ($p=0.007$ and $p=0.004$, respectively) while no significant increase was detected on month 6 and at year 1 ($p>0.05$). In the final control visit, it was found that mean visual acuity was increased by 0.28 logMAR when compared to baseline, indicating statistical significance ($p=.041$). No significant correlation was detected between baseline and final visual acuities.

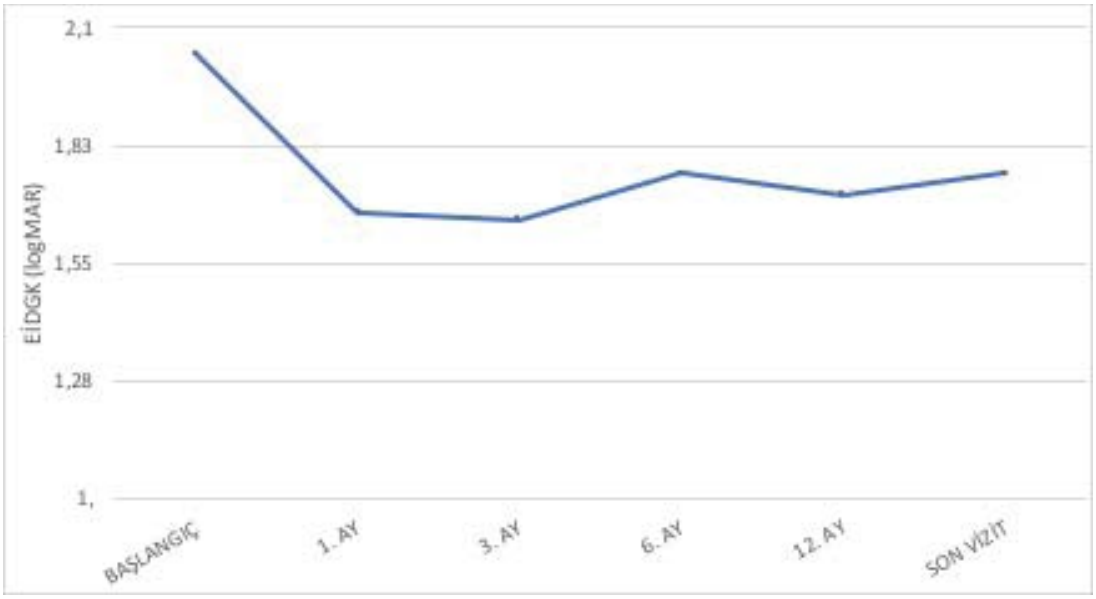

Figure 2: *BCVA changes over months.*

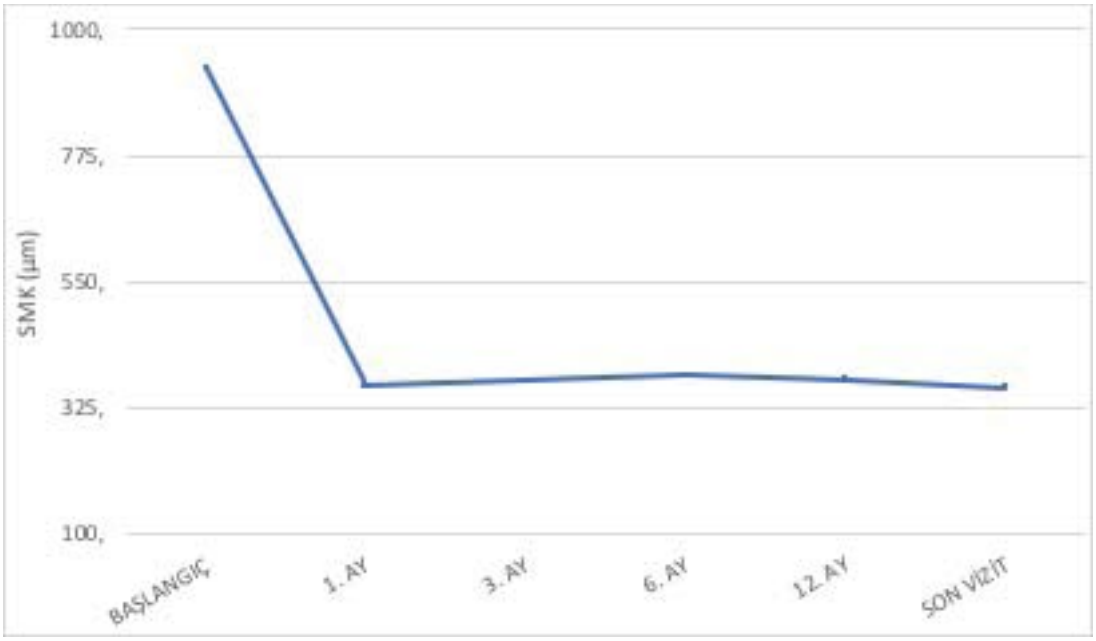

Figure 3: *CMT changes over months.*

It was found that the mean CMT values were 363.5 ± 160.3 (140 - 842) µm on month 1, 371.6 ± 188.5 (146 - 1263) µm on month 3, 381.9 ± 173.1 (0.22 - 3) µm on month 6, 374.2 ± 179.3 (186 - 1145) µm at year 1 and 360.2 ± 184.1 (146 - 1145) µm at final control visit. A significant difference was detected among CMT values obtained at baseline, on month 1, 3, 6 and 12, and at final control visit ($p<0.05$).

DISCUSSION

Submacular hemorrhage is severe condition that threatens central vision in a wide clinical spectrum from younger trauma patients who experienced sudden loss of vision to elder AMD patients who suffered from sudden in addition to progressive loss of vision. Since there is no evidence regarding superiority of one treatment modality to another among current therapies, it is essential to develop a treatment plan by meticulous consideration of prognosis and treatment options by taking individual characteristics of patients into account. Here, we aimed to contribute literature by presenting outcomes of treatment approaches to SMH employed in our clinic. To best of our knowledge, there is no single study that evaluated subretinal hemorrhages resulting from different etiologies in the literature.

In our study, the most common etiology was neovascular AMD (55.6%), followed by PCV (22.2%). In a study including 98 cases with submacular hemorrhage, it was found that PCV (59.2%) and neovascular AMD (30.6%) were most common etiologies in agreement with our study.[8] Similarly, in a study on 99 patients, Juncal et al. reported AMD as most common etiology (80.8%); followed by PCV (8.1%) and RAM (8.1%).[9] Although the relationship between SMH prognosis and underlying disease have been investigated in many studies, as similar to our study, no reliable conclusion could be drawn due to insufficient number of patients in the etiological groups other than AMD.[9,10]

In our study, the mean visual acuity at presentation (2.04 ± 0.80 logMAR), was highly comparable with those (2.08±0.79 logMAR) reported in other studies from Turkey.[11] In studies from different countries, Juncal et al. reported mean visual acuity (2.08±0.9 logMAR) as similar to our study, emphasizing that preoperative visual acuity is an important predictor for postoperative visual acuity.[9] In the study, in agreement with the study by González-López et al., it was indicated that preoperative visual acuity might be guiding in decision-making process for surgery in SMH cases and that benefit from surgery was higher in patients with visual acuity>20/800 at presentation.[9,12] However, no significant correlation was found between mean visual acuity at presentation and final visual acuity in our study.

Among studies on OCT findings of SMH, Hirashima et al. found mean SMH thickness as 557.6 ± 111.3 µm in agreement with our study[13] while, Bae et al. reported mean SMH thickness as 234.4 ± 152.5 µm.[14] Hirashima et al. observed that visual prognosis was better by reduction in SMH thickness but they found no significant correlation (p=0.081).[15] As similar to our study including SMH cases mainly due to AMD, the mean SMH area at presentation was reported as 36.3±27.6 mm^2 in a study including only SMH cases secondary to AMD.[16] However, it was reported as 14.1 ± 10.6 mm^2 in a study including only SMH cases secondary to PCV.[17] Hattenbach et al. evaluated relationship between hemorrhage size and postoperative visual acuity, suggesting no significant correlation.[18] González-López et al. showed that smaller hemorrhage was associated with better final visual acuity, emphasizing that hemorrhage size is an important factor for prognosis.[12] On the other hand, there are studies reporting no significant correlation between final visual acuity and hemorrhage size in the literature.[6,19] Gok et al. found a negative correlation between preoperative SMH thickness and postoperative final visual acuity but the correlation did not reach statistical significance.[20] In our study, the negative correlation between visual acuity gain and preoperative SMH thickness or area was found to be insignificant.

In the literature, there are many studies with contradictory results which investigated effect of time from symptom onset to treatment on prognosis in SMH. Many authors addressed benefit of interventions in chronic SMH[6,21-23] and even the presence of hemorrhage more than 30 days was considered as exclusion criteria in some studies.[24] In a large series including patients underwent vitrectomy, Chang et al. found mean SMH duration as 16 days (1-60 days) and observed a significant improvement in visual acuity after vitrectomy.[26] In addition, in a study including SMH cases with duration>30 days, no significant correlation was found between hemorrhage duration and postoperative visual acuity or success of hemorrhage replacement.[9] In our study, cases with prolonged SMH were also included and a moderate, negative correlation was found between hemorrhage duration and visual acuity gain ($p<0.001$; $r=-0.548$).

Since submacular hemorrhage develops secondary to different etiologies; can have varying sizes; and may be treated by various treatment methods, it is not possible to compare efficacy of different techniques among studies. Guthoff et al. found that addition of bevacizumab injection to intravitreal gas plus t-PA led significant increase in visual acuity when compared to intravitreal gas plus t-PA alone.[27] In support to debate that intravitreal t-PA will not penetrated adequately, Hillenkamp et al. compared groups underwent PPV plus intravitreal or subretinal t-PA, concluding that subretinal t-PA is more successful in replacing location of hemorrhage.[10] Stanesescu-Segall et al. concluded that the highest increase in visual acuity was observed after PPV plus subretinal t-PA and intravitreal gas followed by intravitreal anti-VGEF.[28]

In summary, it was seen that vitrectomy-based methods were used in hemorrhage with larger diameter while less invasive approaches were employed in smaller and restricted hemorrhages in agreement with literature. Since distribution of number of cases was not balanced in different groups of interventions, it was failed to draw reliable conclusions about superiority of different approaches to each other regarding visual prognosis. However, visual prognosis outcomes were promising in the treatments employed. In our study, a significant difference was detected between visual acuity at presentation and on months 1 and 3. In agreement with our study, Juncal et al. found a significant difference between visual acuity at baseline and on postoperative months 1 and 3; however, visual acuity gain was smaller in control visits after month

3.[9] This may be due to achievement of visual acuity gain at early postoperative period by treatment, which decreased due to progression of underlying disease in subsequent controls. However, mean final visual acuity was higher than mean preoperative visual acuity.

In our study, most complications were RD (11.1%), IVH (5.6%) and recurrent SMH (7.4) in agreement with larger series in the literature.[9, 26] In addition, in our study, proportion of cases requiring maintenance of anti-VGEF injections due to findings of postoperative activation (53.7%) was comparable with the study by Juncal et al. (55.6%).[9]

This study has some limitations including retrospective design, lack of control group and poorly balanced groups according to etiology and treatment approaches that did not allow reliable comparison.

CONCLUSION

A significant improvement can be achieved as a result of various surgical approaches in SMH cases due to different etiologies. Time from SMH onset to intervention is an important predictor for final visual acuity.

In order to introduce a standard algorithm in SMH treatment, it is needed to identify certain criteria about characteristics of hemorrhage such as thickness or width based on larger, randomized, controlled studies.

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