Original Article

Real-world outcomes and complications of different surgical approaches for significant submacular haemorrhages

Subhendu Kumar Boral, Deepak Agarwal[1], Arnab Das, Debdulal Chakraborty, Santanu Mandal

Purpose: To evaluate the outcomes and complications after different surgical management of cases with significant sumacular hemorrhage (SMH) of size more than 4 disc diameter (DD). **Methods:** It was a retrospective interventional study. All consecutive 103 cases of significant SMHs were treated by vitrectomy and divided into three groups. In Group A (<4 weeks, confined to the macula or extending inferiorly, $n = 62$), vitrectomy, subretinal cocktail of tissue plasminogen activator (tPA), antivascular endothelial growth factor, and air with SF6 gas; in Group B (4–8 weeks, extending beyond macula, $n = 31$), subretinal tPA followed by SMH drainage either by retinotomy (Group B-1, $n = 17$) or by temporal 180-degree retinectomy (Group B-2, $n = 14$) with silicone oil (SO) tamponade; and in Group C (>8 weeks, extending beyond macula, $n = 10$), SMH removal with autologous retinal pigment epithelium (RPE)-Choroid patch graft transplantations with SO tamponade were performed. Parameters evaluated were best corrected visual acuity (BCVA), Optos, optical computerized tomography, and ultrasonography as required. **Results:** Significant visual improvement was seen from mean preoperative to mean postoperative BCVA in Group A ($P < 0.001$), Group B ($P < 0.001$), and Group C ($P < 0.001$). Postoperative complications were recurrent SMH (4.84% vs 12.90% vs 10%), vitreous hemorrhage (6.45%, GroupA), hyphema (4.84% vs 12.90% vs 10%), hypotony (nil vs 3.23% vs 20%), macular hole formation (6.45%, Group A), epiretinal membrane (16.13%, Group B), and retinal detachment (3.23%, Group A and 10%, Group C). **Conclusion:** Surgical approaches for significant submacular hemorrhage are visually awarding, though certain specific complications may arise.

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Key words: 180-degree retinectomy, autologous RPE-choroid patch graft transplantations, submacular hemorrhage, subretinal rt-plasminogen activator (PA)

Submacular hematoma (SMH) results from the accumulation of blood in subretinal spaces, resulting in destructive shearing of the photoreceptor outer and inner segments and toxic damage by iron, hemosiderin, and ferritin. The important etiologies are neovascular age-related macular degeneration (nAMD), polypoidal choroidal vasculopathy (PCV), ruptured macroaneurysm, trauma, and blood dyscrasias. SMH has been variously classified by many authors, and a consensus is lacking. One way to classify them depends on the size of the bleed. Any SMH less than 1 disc diameter (DD) is considered part of the neovascular component of the choroidal neovascular membrane. SMH can be small (between 1 and 4 DD), medium-sized (at least 4 DD, but does not extend beyond the temporal vascular arcade) and massive (extends beyond the temporal arcades).[1] Multiple treatment modalities have been tried to treat SMHs. Visual outcomes of tPA-assisted subretinal blood removal were first reported by Peyman *et al.* in 1991.[2] Intravitreal injections of anti- vascular endothelial growth factor (VEGF) drugs, pneumatic displacement techniques,[3,4] and intravitreal recombinant tissue plasminogen activator (rtPA) alone[5] have been tried with small submacular hemorrhages. For more significant submacular hemorrhages, the minimally invasive technique of displacing SMH with a combination of intravitreal r-tPA and gas was first described in other studies.[6-8] Other options for more significant hemorrhages were vitrectomy with an injection of subretinal tPA with or without hemorrhage evacuation,[9-15] vitrectomy with intravitreal r-tPA and gas,[16] and vitrectomy with subretinal r-tPA and ranibizumab.[17] A study showed the results of submacular surgery by creating a small retinotomy that may stabilize or improve visual acuity.[18] Also, Kamei *et al.* have reported a favorable visual outcome in 86% of their patients where they used intraoperative perfluorocarbon liquids (PFCL) to displace the SMH after subretinal injection of r-tPA through a smaller retinotomy.[19] Ibanez *et al.* did not observe any significant difference in the visual outcomes in patients undergoing mechanical clot extraction to those in patients undergoing r-tPA-assisted drainage of thick SMH.[20] But Isizaki E showed vitrectomy with removal of subretinal blood by creating temporal peripheral 120-degree retinotomy is effective for massive subretinal hemorrhage.[21] Other options

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have also been advocated like vitrectomy with removal of CNV lesions followed by RPE-choroid patch grafting,[22-28] macular translocation. The outcomes in these cases are varied and depend upon the initial presentation. More extensive subretinal hemorrhage and cases of chronic accumulation of blood are usually associated with poorer outcomes. Intraoperative and postoperative complications following vitreoretinal surgery further hamper visual recovery.

In the present article, the authors tried to retrospectively analyze all the cases of post-nAMD or post-PCV significant submacular hemorrhage with more than 4DD in size, which were managed surgically depending on their duration and distribution and extent of subretinal hemorrhage. The intraoperative and postoperative complications were noted in each intervention, and the real-world outcomes including anatomical outcomes, functional visual recovery, and the complications were evaluated.

Methods

An institutional, retrospective, interventional, nonrandomized study was conducted at a tertiary eye care hospital over the last 8 years. This study involved human subjects, and informed consent was obtained from every patient after being informed about the procedure and its possible complications. This study was approved by the local Ethics Committee and adhered to the tenets of the Declaration of Helsinki.

Cases included were all consecutive post-nAMD or post-PCV significant submacular hematoma cases of more than 4 DD. The total number of cases was 103 eyes of 103 patients. Detailed demographic and clinical parameters were evaluated, including age, sex, eye involved, BCVA, intraocular pressure (IOP), etiology, surgery performed as well as ultra-widefield fundus imaging (whenever possible) by Optos 200TX, optical computerized tomography (OCT) of macula and ultrasonography for posterior segment evaluation as required. A 25-gauge vitrectomy was performed in all. We classified and divided all our cases according to duration and extent into three groups. In Group A (<4 weeks duration, confined to the macula with or without inferior extension, $n = 62$), vitrectomy, subretinal cocktail injection of recombinant tissue plasminogen activator [rt-PA (Actilyse, Boehringer Ingelheim, Germany) 50 µg dosage in 0.05 ml of balanced salt solution (BSS)], anti-VEGF (Ranibizumab 0.5 mg in 0.05 ml), and filtered air (0.03 ml) injection with a 38-gauge flexible/41-gauge metallic needle followed by 20% sulfur hexafluoride (SF6) gas (iso expansile concentration) tamponade. In Group B (4–8 weeks duration, extending both superior and inferior to the macula, $n = 31$), vitrectomy followed by injection of subretinal rt-PA (50 µg in 0.05 ml of BSS) was given and 15–30 min of waiting time was provided for adequate clot lysis. Subretinal blood was then drained either by paramacular retinotomies (Group B-1, $n = 17$), which were a maximum of two in number in opposite quadrants or by temporal 6–7 clock-hours (180-degree or more) retinectomy (Group B-2, $n = 14$), followed by reposition of the retina, laser retinopexy and silicone oil (SO) tamponade. Submacular neovascular tissue was also removed along with SMH in the retinectomy subgroup (Group B-2). PFCL was used to settle the retinal flap in group B-2. In Group C (more than eight week duration, extending both superior and inferior to the macula, $n = 10$), vitrectomy, followed by inducing retinal detachment by injecting BSS by 38G/41G subretinal cannula, then submacular blood removal by creating temporal 6–7 clock-hours (180-degree) retinectomy, followed by harvesting autologous RPE-choroid patch graft from either supero-temporal or inferotemporal quadrant from a relatively healthy-looking area, and transferring the

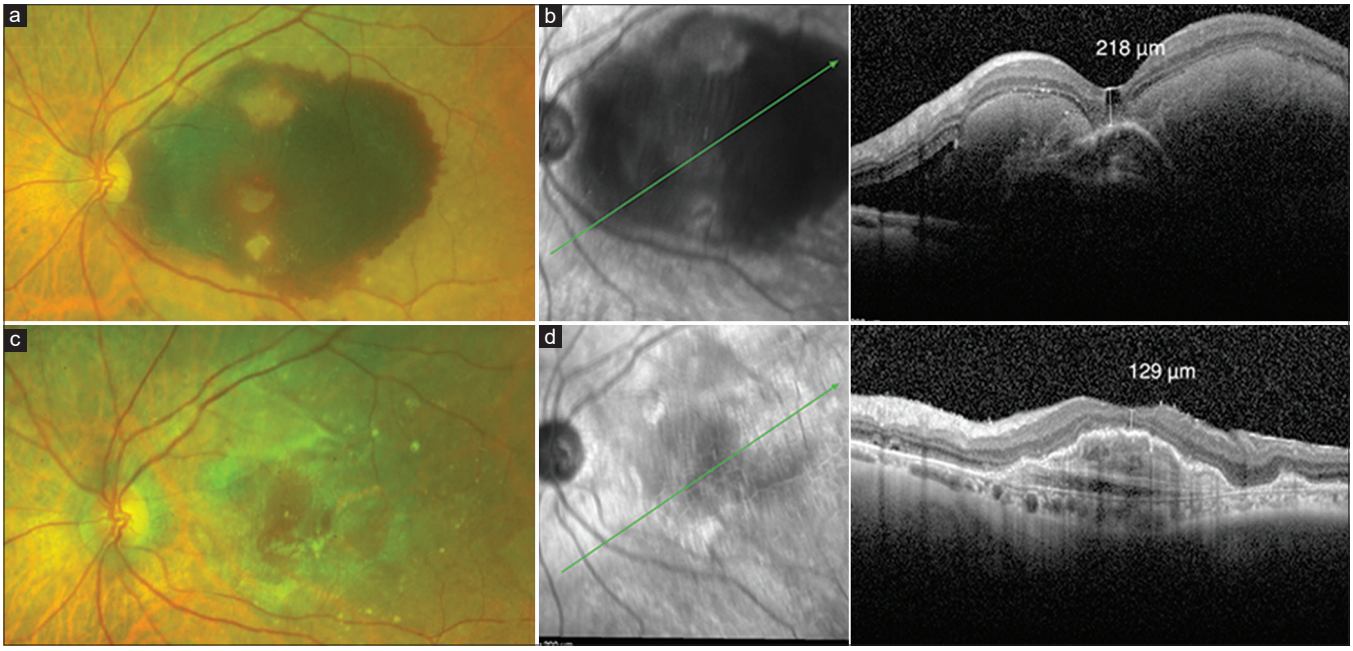

Figure 1: Group A's case of SMH (a) and its preoperative OCT (b) show subneurosensory retinal hemorrhage. Postoperative fundus photograph on Optos at 3 weeks (c) shows nearly resolved SMH along with its corresponding OCT (d), which shows an absence of subneurosensory retinal hemorrhage with decreased pigment epithelial detachment (PED)

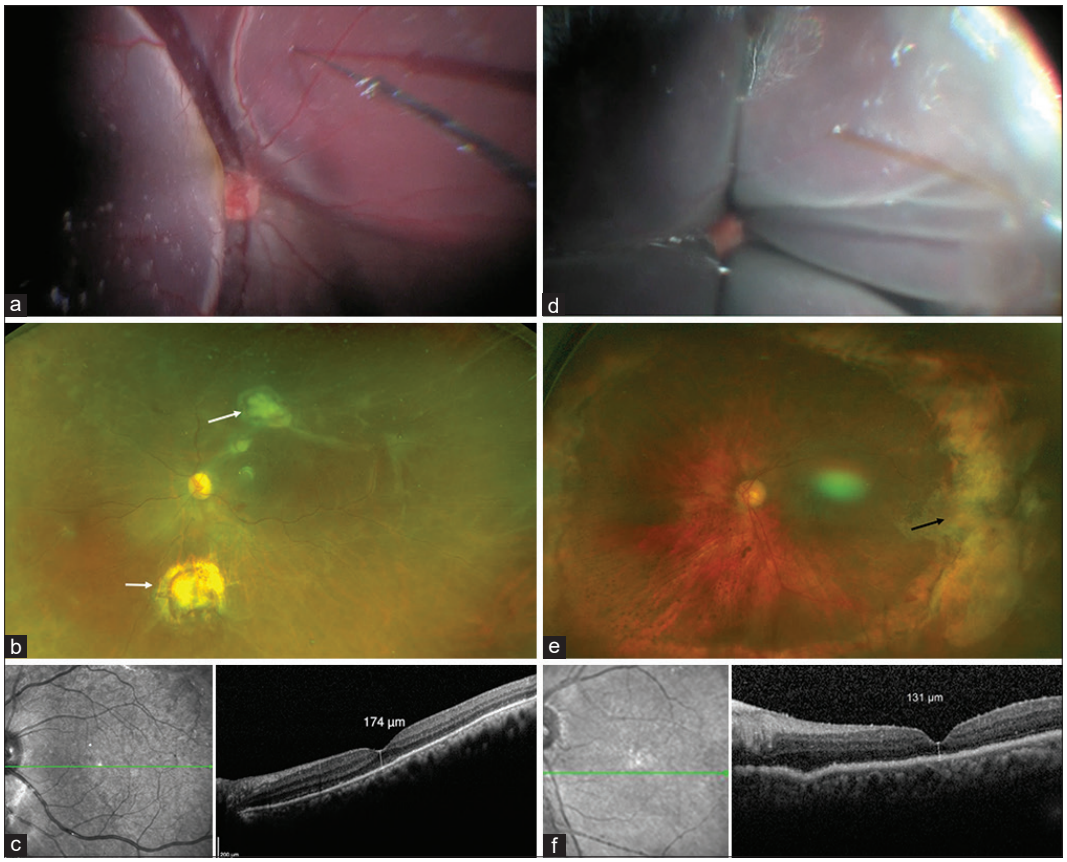

Figure 2: Group B cases: (a) intraoperative still photograph of extensive SMH in the form of hemorrhagic retinal detachment of less than 8 week duration. (b) Postoperative fundus photograph of the same patient after SO removal with scar marks (white arrows) at the sites of retinotomies and its corresponding postoperative OCT (c) which shows complete absence of SMH. (d) Intraoperative still photograph of extensive SMH in the form of hemorrhagic retinal detachment of less than 8 week duration. (e) Postoperative fundus photograph of the same patient after SO removal with attached retina and temporal well-barraged retinectomy site with its corresponding OCT scan (f), which shows complete devoid of SMH

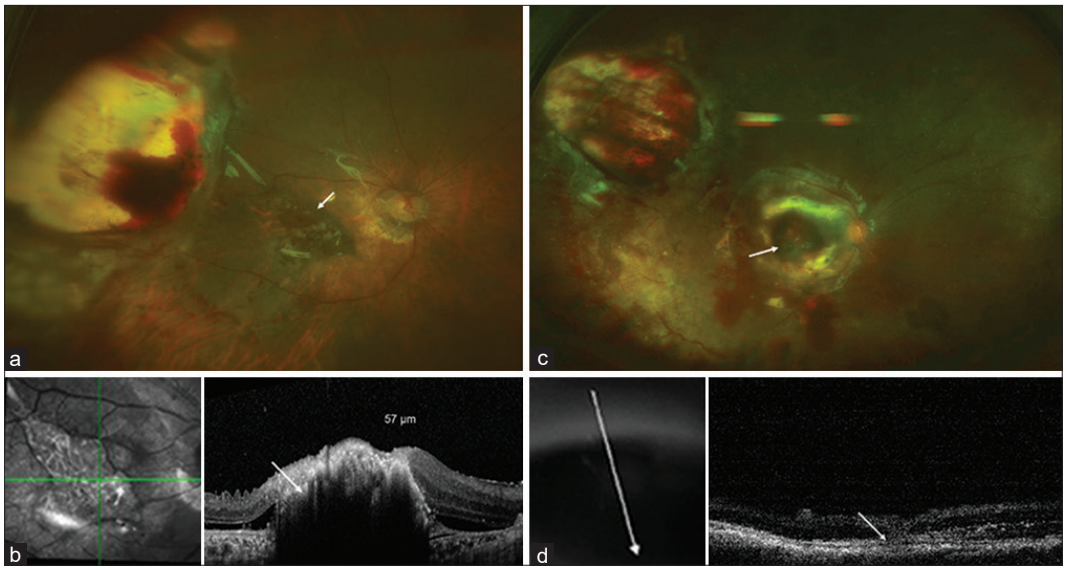

Figure 3: Group C cases: (a) 3 week postoperative fundus photograph with submacular autologous RPE-choroid patch graft *in situ* (white arrow) and (b) its corresponding OCT scan shows subneurosensory retinal RPE-choroid patch graft (white arrow) at the macula. Another case of Group C, where (c) 6 week postoperative fundus photograph with submacular autologous RPE-choroid patch graft *in situ* (white arrow) and (d) its corresponding OCT scan shows subneurosensory retinal RPE-choroid patch graft (white arrow) at the macula

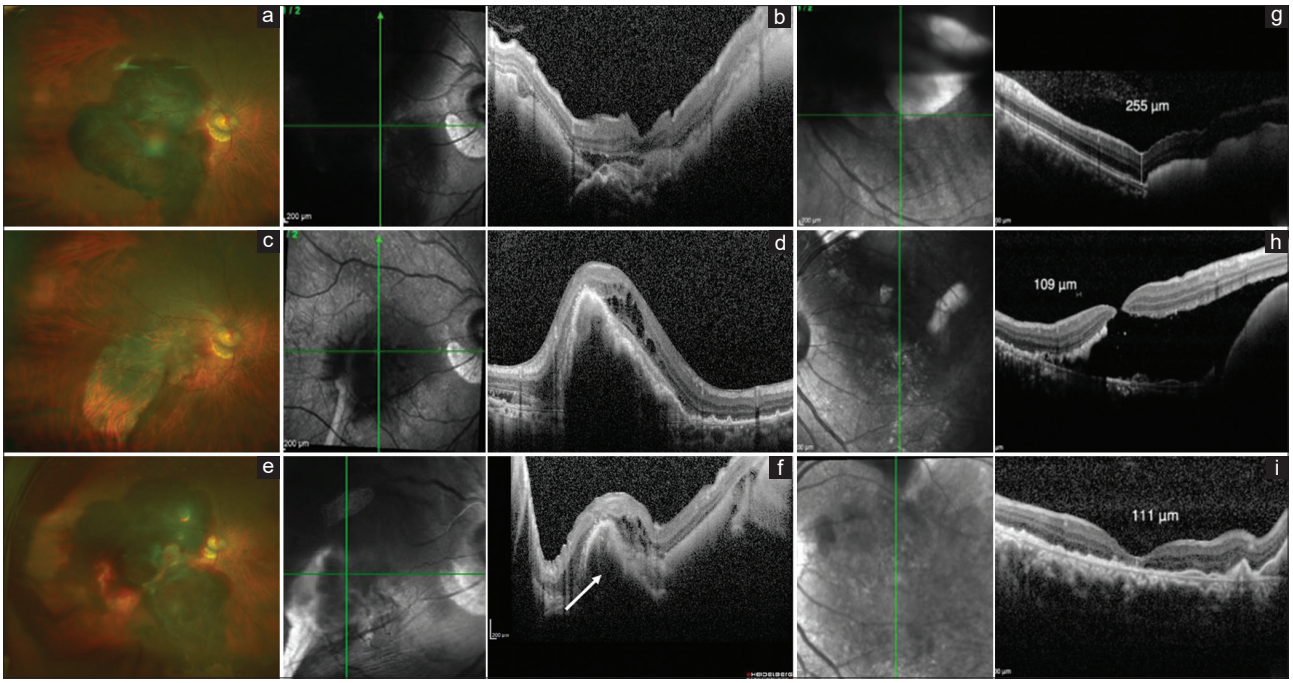

Figure 4: Group A cases: (a) preoperative fundus photograph with SMH, (b) its corresponding OCT scan with SMH, (c) 3 week postoperative fundus photograph of the same patient with complete resolution of SMH, and (d) its corresponding OCT scan with PED and absence of SMH. (e) Recurrence of SMH after 14 weeks of intervention and (f) its corresponding OCT shows markedly elevated SMH. Another patient of Group A cases shows OCT scans (g) preoperative SMH, (h) 3 week postoperative scan shows full-thickness macular hole (white arrow) formation, and (i) closed macular hole, 3 weeks after repeat intervention with peeling the ILM in an inverted flap manner

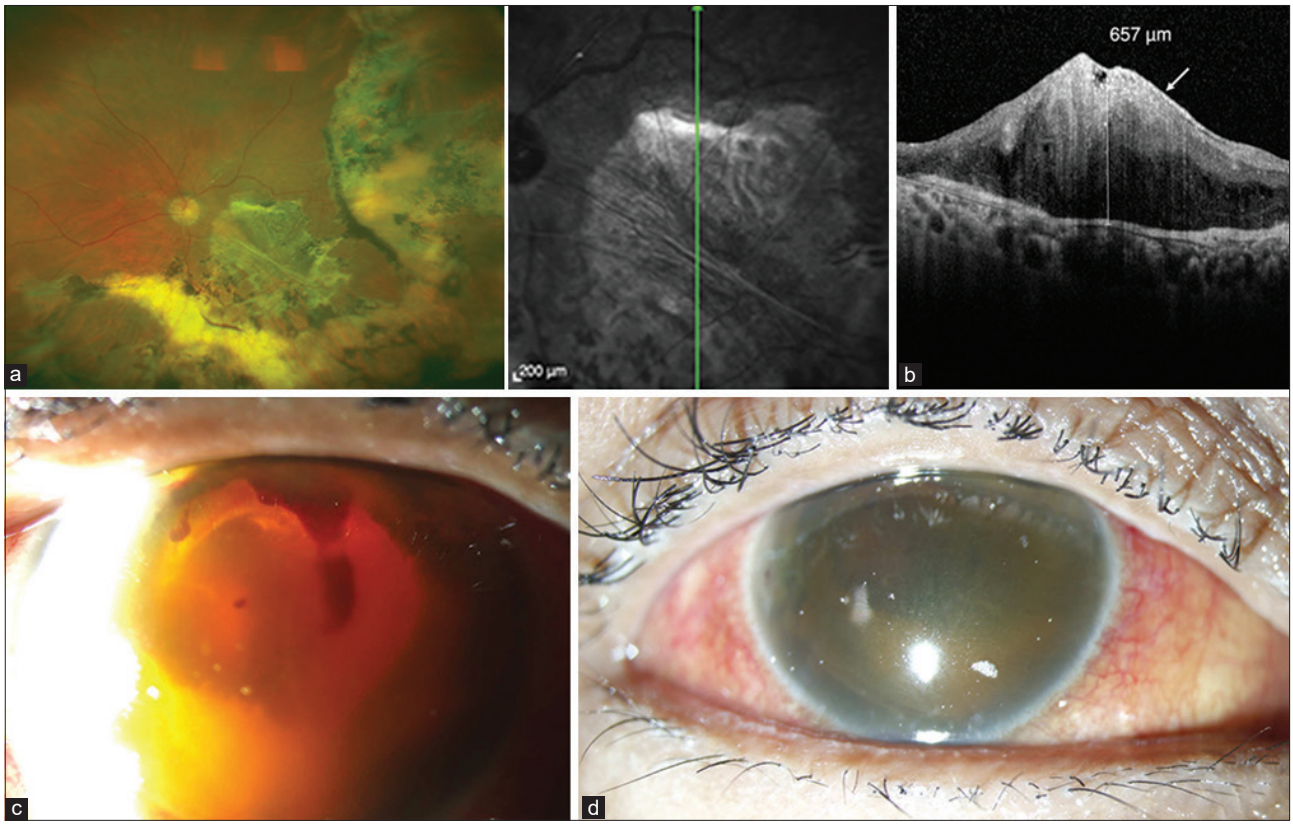

Figure 5: Group B cases: (a) postoperative fundus picture with the trace of thick Epiretinal Membrane (ERM) and (b) its corresponding OCT scan showing tightly adhered ERM with the submacular scar. (c) Postoperative hyphema and (d) postoperative corneal blood staining due to hyphema

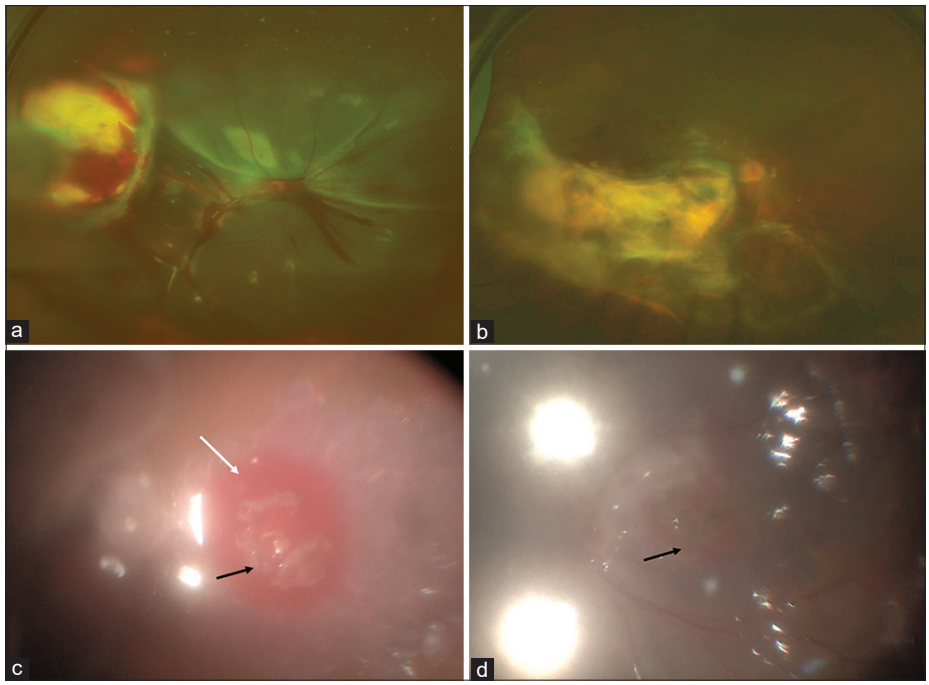

Figure 6: Group C cases: (a) fundus photograph shows postoperative retinal detachment due to PVR. (b) Fundus photograph shows extensive subretinal scar formation extending superotemprally up to the donor site. (c) Intra-operative choroidal hemorrhage from the base of RPE-choroid graft which spontaneously stopped at the end of surgery (d) on raising IOP

Table 1: Comparative incidences of various postoperative complications faced in managing significant submacular hemorrhages in three groups

Table 1a: Group A complications

Study	Recurrent SMH	Hyphema	Vitreous hemorrhage	Macular Hole	RRD	Glaucoma	Phthisis bulbi
Present study	3/62 (4.84%)	3/62 (4.84%)	4/62 (6.45%)	4/62 (6.45%)	2/62 (3.23%)	-	-
González-López *et al.*[17]	13/45 (28.9%)	-	2/45 (4.4%)	1/45 (2.2%)	1/45 (2.2%)	-	-
Wilkins CS *et al.*[15]	4/37 (10.8%)	1/37 (2.7%)	5/37 (13.5%)	-	3/37 (8.1%)	1/37 (2.7%)	1/37 (2.7%)
Haupert CL *et al.*[13]	3/11 (27.27%)	-	-	-	-	-	-
Olivier S *et al.*[14]	1/29 (3.45%)	-	2/29 (6.90%)	-	-	-	-
Chang W *et al.*[11]	6/101 (5.94%)	-	2/101 (1.98%)	-	4/101 (3.96%)	-	-

Table 1b: Group B complications

Study	Recurrent SMH	Hyphema	Vitreous hemorrhage	ERM	RRD	Glaucoma	Hypotony
Present study	4/31 (12.90%)	4/31 (12.90%)	-	5/31 (16.13%)	-	-	1/31 (3.23%)
Thompson JJ *et al.*[30]	-	1/42 (3.7%)	-	-	3.7%(1/42)	-	-
Kamei *et al.*[19]	4/22 (18%)	-	-	3/22 (14%)	3/22 (14%)	-	-
Isizaki E *et al.*[21]	-	-	-	-	3/12 (25%)	1/12 (8.33%)	-

Table 1c: Group C complications

Study	Recurrent SMH	Recurrent CNVM	Hyphema	Vitreous hemorrhage	ERM	Retinal detachment	Hypotony
Present study	1/10 (10%)	-	1/10 (10%)	-	-	1/10 (10%)	2/10 (20%)
Van Meurs JC[23]	-	-	1/42 (3.7%)	-	-	1/42 (3.7%)	-
van Zeeburg EJ *et al.*[24]	4/22 (18%)	-	-	-	3/22 (14%)	3/22 (14%)	8/133 (6%)
Trumer F *et al.*[25]	-	-	-	-	2/10 (20%)	1/10 (10%)	-
MacLaren RE *et al.*[26]	4/11 (36.36%)	-	-	-	-	5/11%(45.45%)	-
Maaijwee K *et al.*[28]	-	11/84 (13.10%)	-	-	-	7/84 (8.33%)	-

graft under the PFCL bimanually to the foveal area. Then, the retinal flap was repositioned using PFCL, followed by laser retinopexy at the margin of retinectomy and 360-degree, then fluid-air exchange (FAE) and SO tamponade (Video 1, Supplemental Digital Content 1). Subretinal rt-PA injection was not used in Group C for clot lysis. We advised 12 h initial propped-up position, followed by a prone position for 14 h a day for the next three weeks in Group A. In Groups B and C, a strict prone position was advised for 16 h a day for the next three weeks.

Inclusion criteria

We included cases of significant SMH cases with more than 4DD size in its longest diameter of either n-AMD or PCV in origin.

Exclusion criteria

We excluded the following situations: i) cases with disc pallor and ii) cases where the perception of light (PL) was absent.

Statistical analysis

SSPS software version 20 was used for statistical analysis. Preoperative and postoperative visual acuities, measured in the Snellen vision chart, were converted into logarithm of minimal angle of resolution (Log MAR) of visual acuity. Student's paired *t*-test was used to evaluate change in BCVA before and after surgical intervention in each group. Visual improvements were evaluated by a two-sample *t*-test. A *P* value less than 0.05 was considered statistically significant.

Results

In total, 103 eyes of 103 patients were included in this study. The mean age of presentation was 64.06 ± 10.18 (range: 40–85) years in Group A, 66.55 ± 10.02 (range 40–81) years in Group B, and 69.1 ± 8.85 (range: 52–84) years in Group C. Fifty-eight patients were male and 45 patients were female. Visual improvements were significant in all three groups. Mean preoperative BCVA LogMAR 2.09 (20/2460) ±0.68 was improved to mean postoperative BCVA LogMAR 0.96 (20/182) ±0.73 in Group A ($P < 0.001$), LogMAR 2.46 (20/5768) ±0.56 to LogMAR 1.50 (20/632) ±0.87 in GroupB ($P < 0.001$), and LogMAR 2.69 (20/9795) ±0.28 to 1.03 (20/214) ±0.28 in Group C ($P < 0.001$). In Group B, small paramacular retinotomies were performed in 17/31 eyes (Group B-1) and temporal 180- degree retinectomy in the rest of 14 eyes (Group B-2). On subgroup analysis between two subgroups of Group B, preoperative BCVA in Group B-1 (retinotomy group) and Group B-2 (retinectomy group) was LogMAR 2.29 ± 0.65 and Log MAR 2.67 ± 0.36, respectively. Independent sample *t*-test showed that the two subgroups were comparable ($P = 0.06$). Postoperative BCVA in both groups was 1.52 ± 0.85 (Group B-1) and 1.48 ± 0.91 (Group B-2), respectively. Independent sample *t*-test also here showed that these two groups were comparable ($P = 0.89$). Combined phacoemulsification with foldable intraocular lens implantation was done along with vitrectomy in 16/62 (25.80%) cases in Group A, 14/31 (45.16%) cases in Group B, and 6/10 (60%) cases in Group C. Twenty-one patients of Group A were phakic and rest of the patients in all three groups were pseudophakic. In Group C, an autologous RPE-Choroid patch graft was taken either from the superotemporal quadrant (eight eyes) or the inferotemporal quadrant (two eyes). Complete displacement of SMH from the macular area with improvement in BCVA was seen in 52/62 (83.87%) eyes in Group A [Fig. 1], 27/31 (87.10%) eyes in Group B [Fig. 2], and 7/10 (70%) eyes in Group C [Fig. 3]. Intraoperatively macular hole formation was detected at the time of subretinal injection of rt-PA in one case of Group A. Further Internal Limiting Membrane (ILM) peeling followed with an inverted flap closed the hole, postoperatively. In Group C, an intraoperative parafoveal macular break was formed during the separation of neovascular tissue from the overlying neurosensory retina in one case, and it had been lasered after retinal reattachment. Intraoperative choroidal hemorrhage around the base of harvested RPE-choroid graft was noticed during its placement at the macula in one case (10%) in Group C, which was spontaneously stopped at the end of surgery on raising IOP. But postoperatively, the distributions of noted complications varied greatly in three groups. Postoperative macular hole formation was noted on OCT in 4/62 (6.45%) eyes, only in Group A. We have to perform repeat interventions to do ILM peeling with an inverted flap technique, followed by gas (SF6) tamponade to close the macular holes [Fig. 4g-i]. Among other postoperative complications, recurrent SMH was noted in 3/62 (4.84%) eyes in Group A [Fig. 4 a-f], 4/31 (12.90%) eyes in Group B and 1/10 (10%) eyes in Group C. Temporal 6–7 clock hour peripheral retinectomy was performed to evacuate recurrent SMH, followed by FAE, laser barrage around the retinectomy margin, and SO tamponade in group A. In groups B and C with recurrent SMH, SO was removed, followed by paramacular retinotomy to remove blood, FAE, and repeat SO tamponade. Hyphema was noted and drained in 3/62 (4.84%) eyes in Group A, 4/31 (12.90%) eyes in Group B, and 1/10 (10%) eyes in Group C. Two cases of hyphema in Group B were associated with corneal blood staining where any further intervention was discouraged [Fig. 5c and d]. Vitreous hemorrhage was noted in 4/62 (6.45%) eyes in Group A for which vitreous lavage was done. Hypotony (IOP less than 8 mm Hg) was not seen in any of the Group A cases, but it was seen in 1/31 (3.23%) eyes in Group B and 2/10 (20%) eyes in Group C. Epiretinal membrane formation was seen in 5/31 (16.13%) eyes in Group B, which were removed during removal of SO [Fig. 5a, b]. Excessive subretinal scarring was seen in one case (10%) in Group C [Fig. 6b]. Postoperative rhegmatogenous retinal detachment (RRD) was seen in 2/62 (3.23%) eyes in Group A and 1/10 (10%) eyes in Group C [Fig. 6a]. Resurgery to settle RD was performed in all. In group A, one case of postoperative RRD was due to a macular hole and we performed peeling of ILM under PFCL with an inverted flap technique and ended up with SO tamponade. The second case of RRD in group A was due to peripheral tear formation, which was also successfully settled with SO tamponade. The case of postoperative RRD in group C was due to proliferative vitreoretinopathy (PVR), where we removed SO, dissected all PVR membranes and settled detached retina under PFCL, performed FAE, removed PFCL, and re-injected SO.

Follow-up: 103 patients had completed follow-up visits, with a mean of 11.12 ± 6.13 months (range of follow-up was 6–39 months).

Discussion

The logistics and algorithm of treating significant submacular hemorrhage cases are still lacking and the preferred

technique is often determined by the extent or duration of the hemorrhage and the surgeon's preference. Different studies followed different management protocols. Rishi E *et al*. found excellent anatomical outcomes with subretinal r-tPA-assisted vitrectomy, but it did not amount to equivalent visual gain.[29] We have followed a more rational logistics to treat the cases with significant submacular hemorrhages. Photoreceptors are mainly affected, and they can withstand the toxic damage till 2–4 weeks after the onset of SMH. We used the nondrainage technique by vitrectomy with a cocktail of subretinal tPA, anti-VEGF (to deliver the drug in the vicinity of the choroidal neovascular membrane and to prevent its early wash-out from the vitreous cavity), and filtered sterile air (to lower the buoyancy of red blood cells, allowing higher gravitational force relative to buoyancy force to facilitate downward displacement of the lysed SMH) injection in cases of SMH up to 4 week duration and mainly confined to macula, as considerable visual improvement is possible without blood drainage because of displacement of submacular blood, either partially or completely. Beyond 4 weeks, when SMH extends beyond macula, both superiorly and inferiorly, it needs drainage technique SMH by evacuation of blood from submacular space either by creating small paramacular retinotomies or temporal 6–7 clock hour peripheral retinectomy. Complete drainage is possible in these cases after clot lysis by subretinal rt-PA injection, to minimize further damage of photoreceptors as well as RPE cell activities. We had advocated full-thickness RPE-choroid graft transplantation to provide relatively healthy autologous RPE cells, when SMH was persisting for more than 8 weeks and extending both superior and inferior to the macula as there was already extensive damage of photoreceptor and RPE cells. Our initial experience of using this technique in long-standing SMHs was encouraging viable options with anatomical and functional improvement as long-term outcomes.[27] A study showed vitrectomy with removal of the subretinal neovascular membrane/hemorrhage complex resulted in better visual results than the displacement of the subretinal hemorrhage,[30] but visual recovery was significant from preoperative to postoperative level in all three groups in our study. We have clubbed the two ways of drainage techniques (less radical retinotomy group B1 and more radical retinectomy Group B2) without RPE-choroid graft transplant in a single group (Group B) to simplify the management strategies. However, on subgroup analysis in Group B, we did not find any difference in visual recovery between B1 and B2 groups. In this present study, we advised maintaining prone position for a longer duration per day and as long as 3 weeks to achieve a better tamponading effect. Intraoperatively, macular hole formation (in one case) and inadvertent intraoperative macular break formation (in one case) happened in groups A and C, respectively. Choroidal hemorrhage around the base of harvested RPE-choroid graft [Fig 6 c & d] in one case (10%) in Group C was unique in our series, as it was not described in other studies. Recurrent SMH was the most important postoperative complication in other studies, and it varied from 3.45% to 28.9% in the nondrainage technique,[11,13-15,17] but it was quite less in Group A, only in 4.84% eyes. Recurrent SMH in the drainage group without RPE-choroid graft transplantation (Group B) was also slightly low in our study, in comparison to the other study (12.90% vs 18%).[19] All recurrent SMH was seen in subgroup B-1 (retinotomy group). Recurrent SMH in cases of SMH drainage with RPE-choroid graft transplantation was evident in 18–36.36% cases[24,26] but only in 10% eyes in Group C. Hyphema was noted in 4.84% eyes in Group A, 12.90% eyes in Group B, and 10% eyes in Group C, which was somewhat higher in other studies.[15,23,30] The incidence of vitreous hemorrhage was noted in 6.45% eyes in Group A, but in other studies, it varies from 1.98% to 13.5%.[11,14,15,17] Hypotony was noted in 13.23% eyes in Group B and 20% eyes in Group C, but in other studies, it was only 6% in cases of drainage with RPE-choroid graft transplantation.[24] The postoperative macular hole was formed in 6.45% eyes in Group A, which was slightly higher than in the other study.[15] In 3/4 postoperative macular hole cases, we injected a subretinal cocktail injection within the macula and outside the macula in one eye. This complication may be subretinal volume overload by cocktail injection and its egress through the fovea, which is the thinnest area of the macula. Epiretinal membrane formation was seen in 16.13% eyes in Group B (four eyes of subgroup B-2 and one eye in subgroup B-1), which was comparable to the other study.[19] Postoperative retinal detachment was seen only in 3.23% eyes in Group A, which was similar to the other study.[16] But in Group C, one eye developed retinal detachment due to postoperative PVR, but in other studies, its incidence varied from 3.7% to 45.45%.[23-26,28] None of our cases of group A and B approaches developed glaucoma postoperatively, though it was a known complication in other studies.[15,21] [Table 1] We recommend that choosing the site for subretinal cocktail injection should be outside the temporal major vascular arcade to avoid iatrogenic macular hole formation and early frequent follow-ups are necessary to prevent blood staining of the cornea in both nondrainage and drainage procedures, although other complications were mostly unavoidable in each category. However, a further multicentric prospective study is required to validate this management approach, considering the possibilities of potential complications.

Conclusion

The present study highlights three different surgical approaches for significant submacular hemorrhage. Each approach is awarded as far as functional and anatomical outcome is concerned. Though there are certain complications, which are mostly specific to a particular surgical approach, these complications can be adequately managed in most cases.

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Conflicts of interest

There are no conflicts of interest.

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