Original Article

Long-term clinical outcomes of submacular blood removal with isolated autologous retinal pigment epithelium-choroid patch graft transplantation in long-standing large-sized submacular hematomas: An Indian experience

Subhendu Kumar Boral, Deepak Agarwal, Arnab Das, Tushar Kanti Sinha

Purpose: To study the outcomes of submacular blood removal with isolated autologous full-thickness retinal pigment epithelial (RPE)-choroid patch graft transplantation in long-standing large-sized submacular hematomas in Indian population. **Methods:** A retrospective study was done on eight consecutive patients of long-standing large-sized submacular hematoma from east India. In all cases, 23G vitrectomy was performed with the induction of retinal detachment (performed with or without 38G or 41G subretinal cannula) and a temporal 180° retinectomy was done. Submacular blood along with choroidal neovascular tissue was removed. A full-thickness RPE-choroid autologous patch graft was taken from a relatively healthy quadrant at the mid periphery and then the graft transferred under perfluorocarbon liquid (PFCL) to place it in the subfoveal area. Then, retina was re-attached using PFCL and laser completed. Silicone oil (5000 cst) was used as a tamponade. Post-operatively, wide-field fundus photographs (Optos), serial optical coherence tomography (OCT), indocyanine green angiography (ICGA), and multifocal electroretinography (ERG) were done. **Results:** The mean age of the patients at presentation was 67.88 ± 10.03 years. Mean pre-operative best corrected visual acquity (BCVA) was 2.64 ± 0.3 log MAR and mean postoperative BCVA was 1.095 ± 0.27 log MAR ($P < 0.05$). The mean follow-up was 20 ± 16.57 months. ICG showed re-vascularization of translocated graft in all at 2 months. Multifocal ERG (after 6 months) showed some waveform in all. None of the cases developed re-bleed. **Conclusion:** Removal of submacular blood and neovascular membrane with autologous RPE-choroid graft is a viable option in cases with long-standing large submacular hematomas.

Key words: 180-degree retinectomy, autologous RPE-choroid patch graft transplantation, silicone oil (5000 centistokes), submacular hematomas

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Submacular hemorrhage (SMH) is a collection of blood between the neurosensory retina and retinal pigment epithelium (RPE) in the macular region. The common causes are neovascular age-related macular degeneration (n-AMD), polypoidal choroidal vasculopathy (PCV), macroaneurysm, trauma, and blood dyscrasias. Hemorrhage less than 1 disc diameter (DD) is considered as a part of choroidal neovascular complex and is not labeled as SMH. A lesion is considered a small SMH when it measures at least 1 DD but less than 4 DDs. A medium-sized SMH extends more than 4 DDs but not beyond temporal vascular arcades, while a large, massive SMH extends beyond the temporal vascular arcade.[1] Hemorrhagic retinal detachment is an extreme form of massive SMH. Y Oshima *et al*. defined the hemorrhagic retinal detachment as a massive subretinal hematoma, extending to the periphery (ora serrata) in more than two quadrants.[2] However, some follow different logistics to classify SMH according to its size.

Severe loss of vision in SMH is because of a barrier effect by the hematoma itself, toxic effects of iron and hemosiderin released by the hemoglobin, destructive shearing of the cells due to fibrin infiltration between the inner and outer segments of photoreceptors, and contraction of the hemorrhage leading to shearing of the outer segments of the photoreceptors. The pathomechanism ultimately causes the formation of submacular fibrotic scar. Visual prognosis depends on the health of the photoreceptors.

In small SMH, intravitreal antivascular endothelial growth factor (VEGF) injection alone or a combination of pneumatic displacement with intravitreal anti-VEGF injection is enough. But medium and larger sized SMH need surgical intervention. Some reported treatment options are subretinal neovascular membrane and hemorrhage removal with forceps,[3] injection of gas without tissue plasminogen activator (tPA),[4,5] injection of intravitreal tPA alone,[6] injection of intravitreal tPA with gas,[7,8] injection of subretinal tPA followed by hemorrhage evacuation[9,10] and vitrectomy with intravitreal injection of tPA with an intraocular gas bubble to help displace the hemorrhage inferiorly.[11] Photoreceptors are relatively healthy

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till two weeks of the onset of SMH. Vitrectomy with subretinal tPA along with subretinal anti-VEGF injection suffices up to 4 weeks, as considerable visual improvement is possible without blood drainage. But the prognosis of long-standing SMH (persisting for more than one month) is poor. Larger SMH does not have a clear treatment algorithm.[12] The submacular surgery trials (SSTs) demonstrated that subretinal surgery with hemorrhage and membrane removal alone was not any better than natural history.[13] But Thompson *et al*. showed that vitrectomy with removal of the subretinal neovascular membrane/hemorrhage complex resulted in better visual results than the displacement of the subretinal hemorrhage.[12] Nguyen-Khoa JL *et al*. showed the results of submacular surgery by creating small retinotomy that may stabilize or improve visual acuity.[14] The reason for poor visual outcome in SST was mainly the loss of RPE, which is essential for retinal function. As a possible alternative, autologous transplantation of choroid and RPE as an option came into the scenario. The surgical technique of transplantation of an autologous free RPE and choroid graft was first described by Peyman *et al*. in 1991.[15] Stanga *et al*. described subfoveal translocation of an autologous RPE-choroid sheet that was cut from the edge of the RPE defect after choroid neovascularization (CNV) extraction.[16] But Van Meurs *et al*. first described subfoveal transplantation of an RPE-choroid patch that was isolated from the mid-periphery.[17]

Large, massive SMH is often followed by a fibrotic response and these cases usually show relative resistance to anti-VEGF injections. The main indications for surgical drainage of SMH are: (a) Large markedly elevated SMH, (b) RPE tear, (c) SMH not responding to the previous treatments, and (d) hemorrhagic retinal detachment (post n-AMD/PCV).

Purpose

The purpose of this study was long-term assessment of the anatomical and functional outcomes of submacular blood removal with isolated autologous full-thickness RPE-choroid patch graft transplantation, in long-standing and large-sized submacular hematoma cases in the Indian population.

Methods

It was a retrospective study of eight consecutive eyes of eight patients where long-standing large-sized submacular hematomas (with or without vitreous hemorrhage) were managed surgically. We enrolled patients who presented to the vitreoretinal services of the hospital between June 2014 and May 2017. This study strictly adhered to the Declaration of Helsinki, and informed consent was obtained from every patient. Approval from the Institutional Review Board (IRB) was taken. We defined the submacular hematomas as large-sized when its extent crossed the macula (beyond the major vascular arcades). Detailed demographic profile of all patients (age, sex), number of intravitreal anti- VEGF injections previously given, clinical diagnosis, pre and postoperative BCVA, surgical procedure done, number of follow-up in months, any additional complication, and silicone oil removal done or not were all noted. All BCVA was converted to logarithm of the minimum angle of resolution (log MAR) for statistical analysis. Poor BCVA that could not be quantified in the Snellen chart was converted into log MAR value according to Wei Y, *et al*. wherein light perception, hand movement, and counting finger were assigned as log MAR 2.9, 2.6, and 2.3, respectively.[18] Postoperative investigations included ultra wide field digital retinal image by Optos 200TX, serial optical coherence tomography (OCT) macular scans, indocyanine green angiography (ICG-A), and multifocal electro retinogram (ERG). OCT scans were performed on either Optovue (Fremont, CA, USA) or Heidelberg Spectralis Spectral Domain OCT (Heidelberg Engineering, Heidelberg, Germany). Fundus autofluorescence had not been performed preoperatively (to assess the quadrant having healthy RPE cells) as vitreous hemorrhage was present in six out of eight cases in our series.

Case selection criteria

We included cases based on the following case selection criteria: i) Long-standing (persisting for more than 1 month), large-sized (more than 4DD and extending beyond the temporal vascular arcade) subretinal hematomas (post age-related macular degeneration or polypoidal choroidal vasculopathy), ii) submacular hematoma not responding to the previous two injections of anti-VEGF and had persisted for more than a month, and iii) Long-standing (more than one month) hemorrhagic retinal detachment (post n-AMD/PCV) with or without vitreous hemorrhage.

Exclusion criteria

We had excluded the following situations i) cases of recent onset subretinal hematomas (less than 1-month duration, as they can be managed by vitrectomy with subretinal or intravitreal tPA injection), and iii) absence of perception of light (PL).

Surgical steps

All the surgeries were performed by a single surgeon. Records showed that the following steps were followed in all [Fig. 1]: a) Triamcinolone-assisted 23G vitrectomy was done using the Constellation Vitrectomy machine (Alcon surgical, Fort Worth, Texas, USA) with the induction of posterior vitreous detachment and completion of vitrectomy. Then, induction of retinal detachment was performed to separate the temporal neurosensory retina from RPE by injecting a balanced salt solution with 38G subretinal cannula [MedOne subretinal 38G Poly Tip Cannula] or 41G subretinal cannula in 3 to 4 areas. Induction of retinal detachment was not performed/needed where retina was already elevated, like in cases of hemorrhagic retinal detachments, b) Temporal 180° retinectomy performed by cutter after cauterization of a temporal peripheral detached retina, close to ora serrata, c) the temporal retinal flap was then everted and kept everted nasally with the help of Tanno's scraper. Then, submacular blood was removed with the help of a cutter, d) choroidal neovascular tissue was separated from subfoveal areas by either end grasping forceps or internal limiting membrane (ILM) forceps keeping the intraocular pressure (IOP) high (30 mmHg or above). Neovascular tissue was removed bimanually (leaving scarred choroid at the subfoveal site) with the help of forceps and vitrectomy cutter using high suction (500 to 600 mmHg) and low cutting rate (1000 cpm or less depending on the thickness and toughness of the scarred neovascular tissue). The bleeding from the choroidal feeder vessels was stopped with endo diathermy, e) PFCL was then injected subretinally to keep the retinal flap away. An approximately 3 mm/2 mm (based on the visual assessment of optic disc size, considering its average diameter to be 1.5 mm) full-thickness RPE-choroid autologous graft (consisting of RPE, Bruch's membrane, choriocapillaris, and choroid) was taken from a relatively healthy-looking quadrant just beyond the mid periphery after performing endodiathermy of the choroid to control choroidal bleeding, f) graft was then transferred unimanually or bimanually under the PFCL with the help of either end grasping forceps or ILM forceps, holding gently at its margin up to the submacular area. The graft was aligned such that RPE side remained up and choroid side remained down at the sub-foveal area. The graft was actually engaged in between the retina and RPE-choroid at the foveal

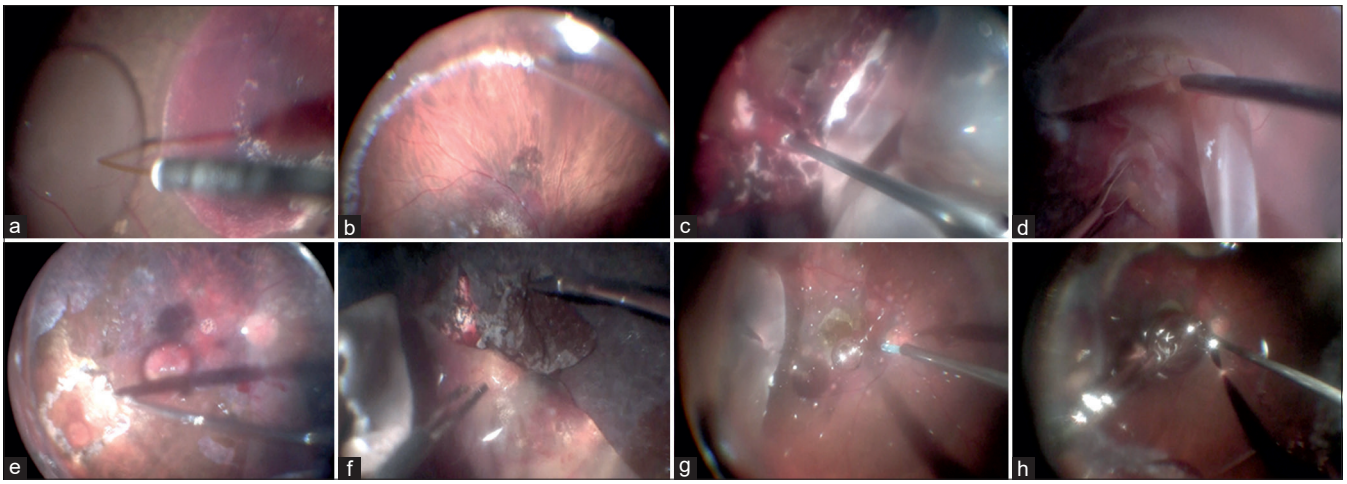

Figure 1: Steps of surgery (a-h)

area to avoid its displacement, g) subretinal PFCL was removed and the retinal flap was re-apposed again by injecting PFCL starting from the central retina up to the retinectomy margin. Fluid air exchange was then started and the retina was settled by aspirating the residual fluid from the retinectomy margin. The laser was done along the margin of retinectomy, peripheral 360 degrees, and around the donor site over retina, h) PFCL was removed and silicone oil (5000 cst) was injected for long-term tamponade. BCVA at 6 months postoperative follow-up was compared with preoperative BCVA for statistical analysis.

Statistical analysis

Statistical analysis was performed in this case series using statistical package for the social science (SPSS) software version 20 (Chicago, Illinois, USA). Mean and standard deviation were evaluated for continuous variables. Paired Student's t-test was used to compare the pre and post-operative BCVA. *P* value of less than 0.05 was considered as statistically significant.

Results

Of the eight eyes of eight consecutive patients, which were operated and been included in our series, six patients were male and two were female. The mean age of the patients at presentation was 67.88 ± 10.03 years. All patients had presented with profound vision loss. Preoperative BCVA was PL and projection of rays (PRs) (both accurate/inaccurate in two quadrants) in 4/8 cases, hand movement in 1/8 cases, and counting finger close to the face in 3/8 cases. Causative diagnosis was either age-related macular degeneration (3/8 patients) or polypoidal choroidal vasculopathy (5/8 patients). Six of 8 cases had vitreous hemorrhage on presentation. In these cases, the detection of sub-RPE hemorrhagic components by ultrasonography (USG) was not possible. However, in case 4 and case 8, the hemorrhage was both subretinal and sub-RPE. In postoperative evaluation, visual improvement was seen in all 8 patients. Mean preoperative BCVA was 2.64 ± 0.3 log MAR and mean postoperative BCVA at 6 months improved to 1.095 ± 0.27 log MAR. Postoperative vision at 6 months, when compared to preoperative BCVA, was statistically significant (*P* value < 0.001) improved. Mean number of prior anti-VEGF (ranibizumab) injections received in our case series was 5.86 ± 6.52 (range 0–16). Clinical characteristics of all 8 patients of submacular blood removal with isolated autologous RPE-choroid graft transplantation have been highlighted in Table 1. Mean follow-up was 20 ± 16.57 months (range 6 months to 53 months). In regards to the donor site selection, in 7/8 cases, RPE-choroid patch graft was harvested from the superotemporal quadrant (STQ) and in only one case, inferotemporal quadrant was chosen (Case 8).

Postoperatively ultra wide field digital retinal image by Optos 200TX showed attached retina with submacular graft, the area from where graft was taken and the laser barrage reaction all around [Figs. 2-4]. On serial OCT macular scan, it was seen that RPE-Choroid graft oedema decreased with follow up and it gradually incorporated with surrounding RPE-Choroidal complex [Figs. 2-4]. Postoperative ICG-A was performed after two months and revascularization of the translocated graft was noted [Fig. 5]. Postoperative multifocal ERG done at 6 months showed grossly reduced parafoveal and perifoveal ring responses. However, all cases showed some central waveforms in the operated eye [Fig. 6].

None of the cases had developed a re-bleed. Silicone oil removal was possible in 5/8 cases at 4 to 6 months after the primary surgery. No intraoperative complications occurred. In the postoperative period, recurrent retinal detachment developed in one case after silicone oil removal (Case 1), where re-surgery was done to settle the retina and silicone oil (5000 cst) was again used for tamponade. Finally, silicone oil was removed in this case 1 year after the re-surgery and the patient maintained log MAR 1 vision. The other postoperative complication noted was excessive subretinal scarring (Case 4), even after the successful removal of the choroidal neovascular membrane. Mean postoperative IOP after primary surgery was 10.25 ± 5.8 mmHg (range 3–19 mmHg). However, persistent hypotony (defined as low IOP below 8 mmHg persisting for more than 6 months) was noticed after primary surgery in 3/8 patients (Case 4, 6, and 7) and in these cases, silicone oil (5000 cst) was not removed. In rest, IOP was well maintained after silicone oil removal.

Discussion

The principle beneficial effects of submacular blood removal are the removal of barrier and toxic effects of submacular collected blood. Removal of choroidal neovascular tissue (fleshy or partially scarred) considerably decreases the possibility of re-bleed. As there is extensive damage of photoreceptor and RPE cells in cases of long-standing large-sized SMH, full-thickness RPE-choroid graft transplantation is justified in these scenarios to provide relatively healthy autologous

Table 1: The clinical characteristics of eight cases of submacular blood removal with autologous RPE-choroid graft transplantation

Age (years)	Sex	Preop BCVA	Preop BCVA (in Log MAR)	Diagnosis	No of intra vitreal anti VEGF Injections	C/F	Surgery done	Postop BCVA (Log MAR)	IOP (NCT) in mm Hg	FU (in months)	Complications	SOR
68	M	FCCF	2.3	AMD	3	Vit He + Sub macular hematoma	Vit + Sub retinal blood removal + RPE-Choroid graft	0.78	17	53	Rec RD	Yes
69	F	PL + PR Accurate	2.9	PCV	5	-do-	-do-	1	19	15	-	Yes
84	M	FCCF	2.3	AMD	14	-do-	-do-	0.78	12	6	-	Yes
71	M	HMCF	2.6	PCV	3	IMSC + Large submacular hematoma	-do- along with Phaco IOL	1.4	3	32	Excessive sub retinal scarring + Persistent hypotony	No
75	M	PL + PR inaccurate	2.9	PCV	Nil	Vit Hge + Hemorrhagic RD	-do-	1.4	10	12	-	Yes
68	M	FCCF	2.3	PCV	16	Vit He + Sub macular hematoma	-do-	1	6	8	Persistent hypotony	No
52	F	PL + PR inaccurate	2.9	PCV	Nil	IMSC + Vit He + Hemorrhagic RD	-do- along with Phaco IOL	1.4	4	22	Persistent hypotony	No
59	M	PL + PR Accurate	2.9	AMD	3	Sub macular hematoma	-do-	1	11	6	-	Yes

PCV=Polypoidal Choroidal Vasculopathy; AMD=Age related Macular Degeneration; M=Male; F=Female, Preop=Preoperative, Postop=Postoperative, C/F=Clinical features, FU=Follow up, SOR=Silicone oil removal, Vit Hge=Vitreous haemorrhage, Rec RD=Recurrent retinal detachment

RPE cells. Vitrectomy with subretinal tPA with or without sub retinal anti-VEGF may not work here and functional improvement is hardly possible. Mac Laren RE *et al*. showed that autologous RPE transplantation can in principle restore vision in neovascular AMD, but surgical complications remain high.[19] Van Zeeburg EJ *et al*. have seen that more gain in visual acuity might be possible for patients with a graft than anti-VEGF treatment in the absence of complications.[20] Cereda *et al*. showed that the creation of a full-thickness RPE-choroid flap through a 180° peripheral retinotomy is feasible and safe.[21] Maaijwee K *et al*. showed an autologous free RPE-choroid graft may stabilize or improve vision up to 4 years after surgery.[22] Our study also showed that submacular blood removal and full-thickness RPE-choroid graft is a viable option in cases with severe vision loss due to SMH. Postoperative visual recovery, though quantitatively moderate, was still considerable in comparison to preoperative profound loss of vision. The log MAR visual acuity improved from a preoperative level of 2.64 ± 0.3 to a postoperative level of 1.095 ± 0.27 (P value < 0.001). Six of 8 cases had a vitreous hemorrhage on presentation, where detection of sub-RPE hemorrhagic component by USG was not possible. For this same reason, it was not possible to perform autofluorescence to assess the quadrant having healthy RPE cells. There is an obvious loss of diseased RPE layer from the macular area during the removal of submacular blood along with submacular neovascular tissue. However, by providing relatively healthy RPE-choroid patch graft to the macular area after harvesting from the temporal periphery, this approach resulted in improvement in anatomical and significant functional outcomes finally, especially in 5/8 cases (Case 1, 2, 3, 6, and 8).

Hemorrhagic retinal detachments (defined as massive subretinal hematoma, extending till ora serrata) were seen in 2/8 cases, which may be due to their late presentation. They presented with vision PL + and PR inaccurate in two quadrants and had not received any prior anti-VEGF injection or photodynamic therapy (PDT). Extremely advanced situations with a poor visual prognosis like these gained ambulatory vision after surgery.

We preferred a larger graft (3 mm/2 mm) to provide more RPE cells as well as to compensate for future graft shrinkage. We chose a relatively healthy-looking quadrant abundant with uniformly pigmented RPE layer just beyond the mid periphery. In 7/8 cases, the donor site was superotemporal quadrant (STQ) and in one case it was inferotemporal quadrant (Case 8, as extensive loss of RPE, was detected at STQ during surgery).

Previous studies showed that the rate of complications like retinal detachment is high.[18,21] The present study has 1/8 (12.5%) incidence of post-op retinal detachment while the study by McLaren has 7/84 (8.33%).[19] The incidence in this study is marginally more than the reported series. We faced persistent low IOP (IOP less than 8 mmHg) as a major postoperative complication in 3 out of 8 eyes in our case series. Van Zeeburg *et al*. also faced hypotony in 2/125 cases after silicone oil removal and in 8/133 cases, silicone oil was not removed to prevent hypotony.[23] Probable reasons for this high incidence of persistently low IOP in our case series, even after 6 months from the primary surgery were large areas of retinectomy, exposed peripheral RPE-choroid, and ciliary body fibrosis. However, we have operated on more advanced and long-standing cases than previous studies.[23] Excessive subretinal scarring happened in only one eye (case 4). Recurrence of subretinal hemorrhage was not seen in any case, while it was a major complication in some studies. Maaijwee *et al*. found subretinal hemorrhage in seven

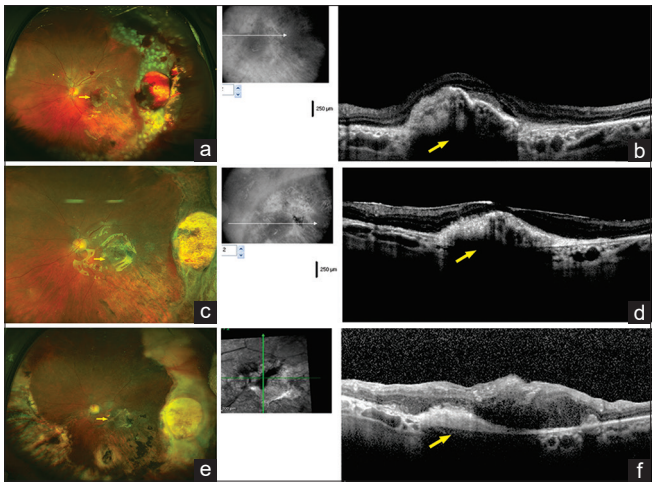

Figure 2: Postoperative submacular autologous RPE-choroid graft (yellow arrows) with a gradual decrease in graft edema in serial OCTs in Case 1 at 2 weeks (a and b), 3 months (c and d), and 53 months (e and f)

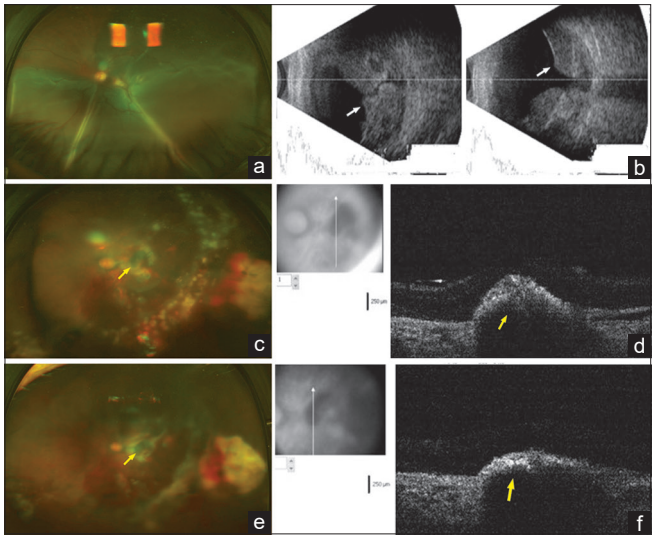

Figure 4: Preoperative optos (a) and B-scan ultrasonography (b) showing hemorrhagic retinal detachment (white arrows) with vitreous hemorrhage in case 5. Postoperative submacular autologous RPE-choroid graft with a gradual decrease in graft edema in serial OCTs (yellow arrows) at 2 weeks (c and d) and 4 weeks (e and f)

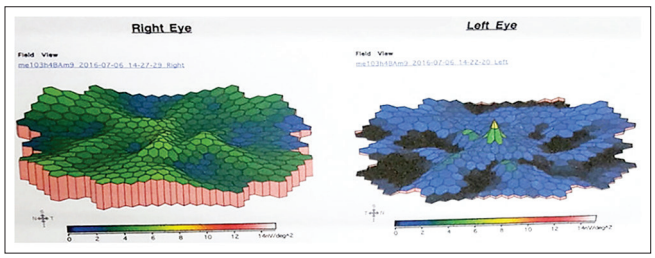

Figure 6: Multifocal ERG after 6 months showed some waveform in operated left eye

cases, subretinal and vitreous hemorrhage in one case and one suprachoroidal hemorrhage.[22] None of the RPE-choroid harvest sites showed significant bleed. Thus, our study indirectly reflected that complete removal of neovascular tissue decreases the possibility of re-bleed.

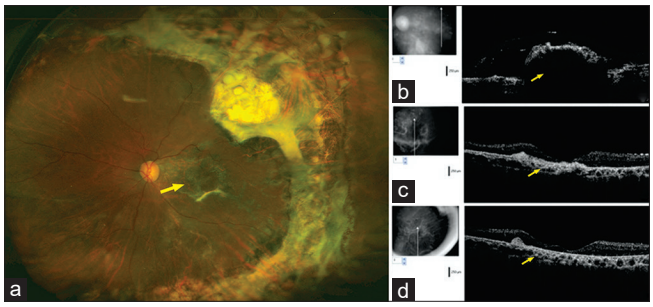

Figure 3: Postoperative submacular autologous RPE-choroid graft depicted by yellow arrows (a) with a gradual decrease in graft edema in serial OCTs at immediate postoperative stage (b), at 3.5 months (c) and at 9 months after silicone oil removal (d) in Case 2

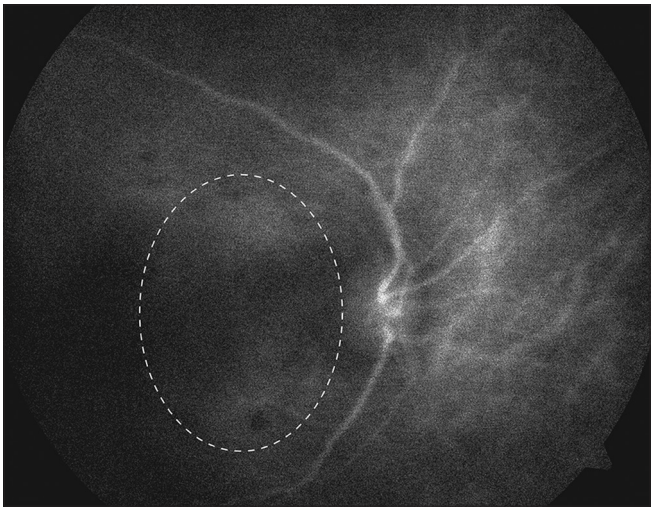

Figure 5: ICG angiography showed revascularization of the translocated graft (highlighted within the white dotted line) at 2 months

Usually, revascularization occurs in translocated RPE choroid graft by new feeder vessels over several weeks as demonstrated in ICG angiography. Maajijwee *et al*. observed graft reperfusion in 29/31 patients on ICG[24] and this reflects as the anatomical viability of the graft. In this study, ICG showed reperfusion of RPE-choroid graft after 2 months.

Moreover, functional viability of the graft was assessed by performing postoperative multifocal ERG. The presence of some wave pattern formation in ERG, even if with low amplitude spikes denoted that the transplanted autologous graft was functioning. Assessment by postoperative mf-ERG was not done in previous studies. A few studies showed the role of microperimetry to judge the fixation after surgery, but unfortunately, microperimetry was not available in our settings. Hence, we cannot categorically comment on the recovery of foveal function.

Limitation in our study was the small sample size, which limits significant quantitative and comparative detailed data analysis. This approach should be considered in selective cases like long-standing large-sized SMH. This stringent selection criterion makes enrolling of a large number of patients difficult.

Conclusion

This study shows that removal of submacular blood and neovascular membrane with autologous RPE-choroid graft is a viable option in cases with long-standing large-sized

submacular hematomas, with both anatomical and functional improvement possible as a long-term outcome.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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