

Surgical Management of Subretinal Hemorrhage

Ecem ONDER TOKUC¹, V. Levent KARABAS²

ABSTRACT

Large submacular hemorrhage, an uncommon manifestation of neovascular age-related macular degeneration. Submacular hemorrhage damages photoreceptors due to iron toxicity and reduced nutrient flux. Multiple treatment modalities have been suggested including intravitreal anti-vascular endothelial growth factor injections, pneumatic displacement with or without adjuvant intravitreal tissue plasminogen activator, and pars plana vitrectomy with or without adjuvant subretinal tissue plasminogen activator, macular translocation or RPE-choroidal patch graft. While no consensus exists, the preferred technique is often determined by the extent or duration of the hemorrhage and surgeon preference. In this review, surgical treatments will be discussed in submacular hemorrhage.

Keywords: Subretinal hemorrhage, Pneumatic displacement, Subretinal tPa, Macular translocation, RPE – choroidal patch graft.

INTRODUCTION

Subretinal hemorrhage can result from abnormal vascularization in retina and choroidal circulation or trauma or macro-aneurysm. Age-related macular degeneration, ocular histoplasmosis, high myopia, retinal arterial macro-aneurysm and trauma are among reasons leading severe subretinal hemorrhage¹.

Submacular hemorrhage results in photoreceptor injury within approximately 24 hours. This may lead irreversible damage in outer retinal layers within 3 days². In animal experiments, it was shown that photoreceptor injury can start within one hour after hemorrhage³. Macular damage secondary to submacular hemorrhage develops through multiple mechanisms. Free iron released with bleeding, fibrin and hemosiderin cause oxidative stress. The blood accumulated at subretinal area disrupts nutrient exchange between retinal pigment epithelium and outer retinal layer. The clot contracted causes mechanical injury in photoreceptors⁴. The clot contracted at subretinal distance can lead avulsion in photoreceptors over time^{6,7}. Thus, vitreoretinal surgeon should be careful when removing clot at subretinal space.

Macrophage and fibroblast chemotaxis to injured area lead release of inflammatory molecules, fibrin formation

and scar development at advanced stage. Disciform scar causes atrophy in neurosensory retina by time^{2,3}.

1. PROGNOSTIC FACTORS

The prognosis is poor in the natural history of submacular hemorrhage. The visual acuity ranges from light perception to 20/200 in the patient⁴. Visual prognosis depends on visual acuity at baseline, extent of hemorrhage and time to treatment. Concurrent anterior and posterior segment involvement has negative effect on prognosis^{8,9,10}.

The extent of hemorrhagic area, thickness of submacular hemorrhage and hemorrhage duration before treatment seems to be three primary factors influencing on prognosis..

1.1. Extent of Hemorrhagic Area

Subretinal lesions are generally classified according to extent of lesion as follows:

- Small – Lesions at least one disc diameter (DD) in size but smaller than 4 DD¹¹
- Moderate – Lesions at least 4 DD in size but do not extend beyond temporal vascular arcades¹¹
- Large – Lesions extending beyond temporal vascular arcades but not equator¹¹

1- Ophthalmologist, Ophthalmology Department of Kocaeli University, Medicine School, Kocaeli, Turkey

2- Prof. MD., Ophthalmology Department of Kocaeli University, Medicine School, Kocaeli, Turkey

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Correspondence Address:

Levent KARABAS

Ophthalmology Department of Kocaeli University, Medicine School, Kocaeli, Turkey

Phone: +90 542 587 9635

E-mail: dreecem@yandex.com

- Extremely large— Lesions extending beyond equator in at least two quadrants^{12,13}

Thick subfoveal hemorrhage, generally measured as >500 μm in thickness, are defined as blood under fovea causing apparent elevation of retina and opacification of RPE on fundus examination^{11,14}.

There are studies showing a negative correlation between submacular hemorrhage area and final visual acuity. Scupola and Arvey proposed that increased subretinal hemorrhage area was correlated to poor visual prognosis^{1,15}. However, there are studies advocating that there is no correlation between hemorrhage area and visual prognosis¹⁶.

1.2. Thickness of Submacular Hemorrhage

Poor visual prognosis at long-term has been linked to increased submacular hemorrhage thickness. This can be explained by increased diffusion distance between photoreceptors and other layers and nutritional failure. The blood caused photoreceptor atrophy over time by blocking diffusion between outer retinal layers and RPE^{15,16,17}.

1.3. Hemorrhage Duration

Submacular hemorrhage duration and final visual acuity displays inverse proportion. Long-term exposure of photoreceptors to hemorrhage leads to iron toxicity and atrophy. Recurrent bleedings worsen visual prognosis⁵. In the literature, it was suggested that prolonged submacular hemorrhage is linked to irreversible retinal injury⁴. Levis et al. observed poorer visual outcomes in submacular hemorrhage more than 7 days¹⁸. In a study Hattenbach et al., better visual outcomes were reported in submacular hemorrhage that underwent surgery within 2 weeks¹⁹.

Use of systemic drugs should have to be considered during follow-up. In a study by Kieran et al., daily use of aspirin, clopidogrel and warfarin increases the risk for submacular hemorrhage and vitreous hemorrhage in patients with age-related macular degeneration²⁰.

The optic coherence tomography (OCT) can be used to determine prognostic factors such as integrity of inner and outer retinal segments, submacular hemorrhage area and foveal thickness. During follow-up, OCT can be helpful to assess other prognostic factors such as decrease in submacular hemorrhage and choroid rupture and RPE integrity^{10,22}.

2. TREATMENT

In submacular hemorrhage, there are many treatment modalities including follow-up alone, anti-VGEF (vascular

endothelial growth factor), tissue-plasminogen activator (tPa), intravitreal gas administration and vitrectomy (macular translocation, RPE-choroid patch graft, subretinal tPa injection, drainage of submacular hemorrhage).

2.1. Pneumatic Displacement and Intravitreal tPa

In 1996, for the first time, Heriot reported successful use of intravitreal tPa and gas (perfluoropropane or sulfur hexafluoride) injection for pneumatic displacement of hemorrhage in subretinal hemorrhage related to age-related macular degeneration²².

Hassan et al. reported that submacular hemorrhage was recovered within 5 days in all of fourteen patients who were treated with intravitreal tPa (25-100 μg) and expandable gas injection and followed by prone positioning. It was reported that 67% of patients had ≥ 2 lines gain in Snellen cards in final control. No tPa-related toxicity was observed in the study⁵.

In a retrospective study on 104 patients, Chen et al. used intravitreal tPa (100 μg) and expandable gas injection. It was seen that there was ≥ 2 lines visual acuity gain in 64% of patients at 3-months follow-up. In the study, mean time from onset of submacular hemorrhage to surgery was found as 9.3 days. In the study, it was reported that age-related macular degeneration was most common cause of submacular hemorrhage; however, prognosis was better in patients with submacular hemorrhage due to causes other than age-related macular degeneration²³.

There are studies in which pneumatic displacement alone without intravitreal tPa injection as initial treatment. Ohji et al. injected pure perfluoropropane gas (0.4-0.5) to 5 patients with submacular hemorrhage caused by age-related macular degeneration. Complete displacement was observed in 3 patients while partial displacement in remaining 2 patients. In the study, it was suggested pneumatic displacement may result in better visual acuity when it is used as monotherapy in short-term submacular hemorrhage²⁴.

Gopalakrishnan et al. used pneumatic displacement without tPa and maintained prone position in 20 patients. It was reported that subretinal hemorrhage was displaced, either completely or partially, in 40% of patients. Authors suggested that visual outcomes could be poorer in submacular hemorrhage secondary to age-related macular degeneration. It was concluded that pneumatic displacement alone without tPa may fail in submacular hemorrhage secondary to age-related macular degeneration²⁵.

In a patient with subretinal hemorrhage and treated

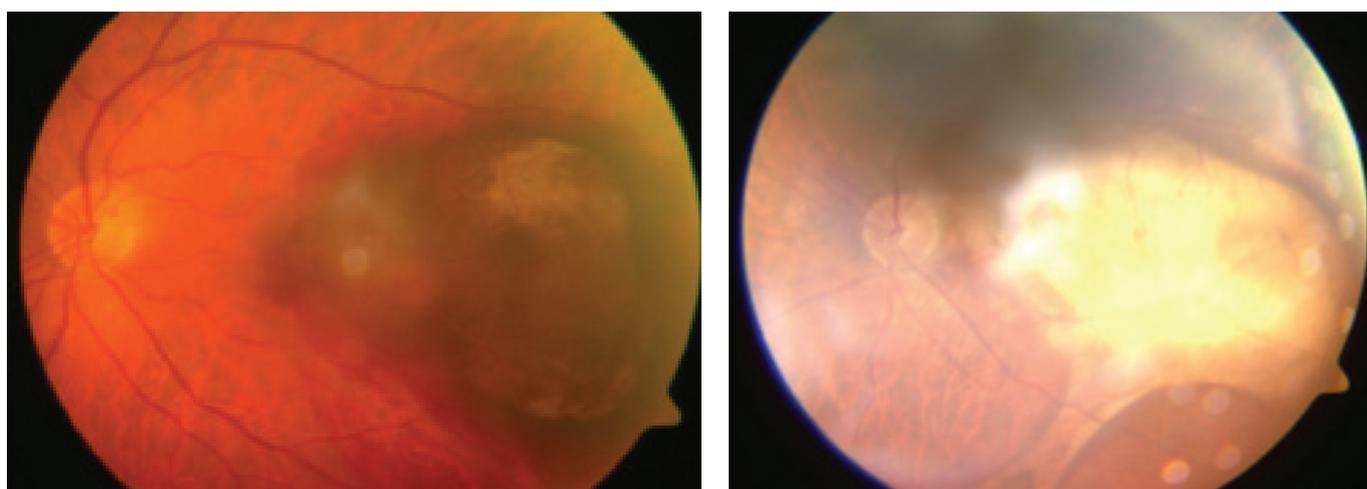
with pneumatic displacement alone (using SF6) without tPA administration, we observed that visual acuity was improved in short-term; however, it was decreased at long-term. Poorer visual anatomic outcomes are observed in the natural course of the disease (Picture 1a, b).

In a study on 21 patient with submacular hemorrhage duration <10 days, Cakir et al. administered tPA 24 hours after perfluoropropane gas injection in 7 patients. It was reported that submacular hemorrhage was displaced in all but one patient within 7 days and that intravitreal tPA use did not cause difference in visual acuity²⁶.

Potential complications include vitreous hemorrhage, retinal detachment and recurrence of submacular hemorrhage in pneumatic displacement⁵.

There are many studies using pneumatic displacement in combination with intraretinal or subretinal tPA. Table 1 summarized outcomes in these studies¹¹.

It is possible that pneumatic displacement alone using intravitreal gas without vitrectomy can be successful in early submacular hemorrhage. It is more likely to fail in clotted subretinal hemorrhage.



Picture 1a,b. Sufficient displacement could not be achieved by 0.4 cc pure SF6 gas alone in a patient with wide and thick hemorrhage and it was resulted with extended scar and visual acuity of hand movement at long-term.

Table 1. Outcomes of studies using pneumatic displacement alone or in combination with other techniques.

Treatment	Patient (n)	Mean age	Mean (median) VA at baseline: logMAR (HS)	Mean VA at baseline: logMAR (HS) Snellen values	Final mean (median) VA at baseline: logMAR (HS) Snellen values	Final mean VA at baseline: logMAR (HS) Snellen values	VA improvement % (HS)	VA worsening % (HS)	2 lines VA gain in Snellen or equivalent	2 lines VA in Snellen or equivalent % (HS)	Final VA ≤20/200 (HS)
IVT anti-VEGF	109	72	0.96 (83); 20/182	0.93 (86); 20/170	0.76 (83); 20/115	0.81 (86); 20/126	62 (82)	30 (82)	27 (52)	7 (52)	45 (22)
IVT TPA + gas	206	73	1.43 (74); 20/536	1.46 (206); 20/576	1.02 (74); 20/209	1.00 (206); 20/200	54 (206)	16 (206)	44 (171)	7 (171)	56 (149)
IVT anti-VEGF+ gas	30	71	1.35 (30); 20/447	1.35 (30); 20/447	1.35 (30); 20/447	0.86 (30); 20/144	70 (17)	23 (17)	59 (17)	12 (17)	59 (17)
IVT gas	88	72	1.52 (88); 20/662	1.56 (88); 20/726	1.20 (88); 20/316	1.21 (88); 20/324	62 (72)	18 (72)	50 (72)	7 (72)	52 (72)
IVT anti-VEGF + gas + TPA	58	69	1.00 (28); 20/200	0.84 (58); 20/138	0.70 (28); 20/100	0.52 (58); 20/66	80 (40)	15 (40)	37 (59)	5 (40)	70 (20)
PPV + gas + TPA	88	74	1.10 (41); 20/251	1.15 (88); 20/282	1.20 (41); 20/316	1.19 (88); 20/309	63 (99)	23 (99)	61 (41)	34 (41)	48 (41)
PPV + subretinal TPA and VEGF	43	78		1.16 (45); 20/294		0.88 (43); 20/151	76 (28)	7 (28)	-	-	38(26)
PPV + gas + anti-VEGF + TPA	59	72	1.70 (15); 20/1002	1.68 (59); 20/1043	1.30 (15); 20/399	0.86 (59); 20/171	82 (59)	0 (23)	91 (21/23)	0 (23)	45 (11)

IVT: Intravitreal, VEGF: vascular endothelial growth factor, PPV: pars plana vitrectomy, VA: visual acuity.) (Stanescu-Segall D et al.¹¹)

2.2. Pars Plana Vitrectomy, Subretinal tPa and Gas Injection

Many clinician employ tPa as an adjunct to resolve clot in the treatment of submacular hemorrhage. The lysis of clot using tPa eliminates the need for larger retinotomy to remove clot. Fibrin lysis reduces risk for iatrogenic retinal detachment and proliferative vitreoretinopathy (PVR) as well as photoreceptor injury that may occur during clot removal and makes the patient eligible for pneumatic displacement¹¹.

Hauptert et al. injected tPa to subretinal area using 36 G cannula. Authors achieved clot lysis by tPa while clot displacement by fluid-gas exchange and maintaining prone position at postoperative period²⁷.

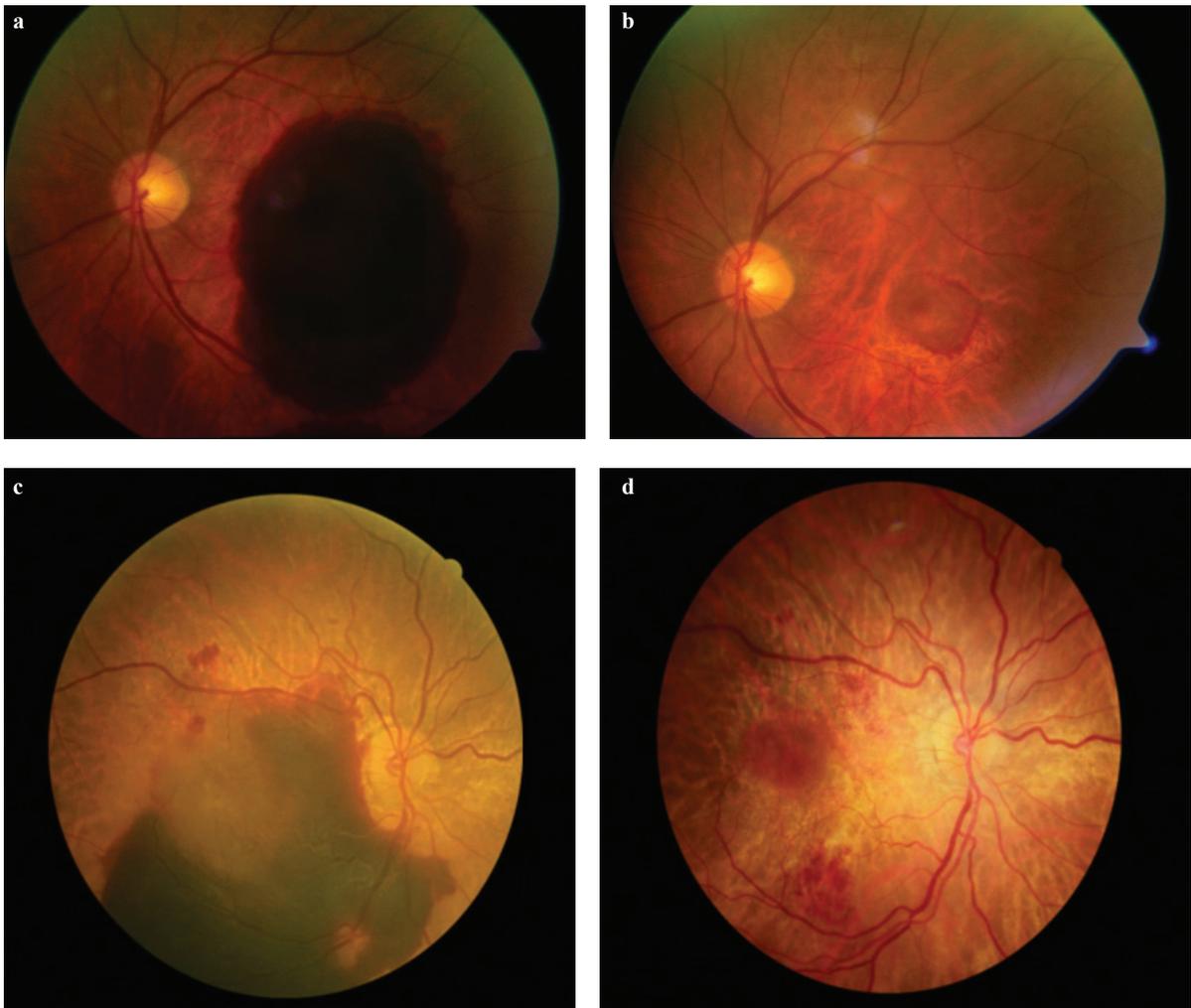
Mahmoud et al. injected combination of tPa (0.4 ml, 50 μ), bevacizumab (0.1 ml, 2.5 mg) and filtered air by using 41 G cannula. The aim of subretinal air is to facilitate displacement of hemorrhage. This is followed by intravitreal air-fluid exchange. Air aided to removal

of condensed clot from macular region by facilitating displacement²⁸.

Kapran et al. used PPV plus subretinal PPV using 41 G cannula in 10 patients with subretinal hemorrhage. At the end of study, it was reported that preoperative and postoperative visual acuity was 1.75 and 1.23 logMAR, respectively. It was also reported that there was at least 3 lines of visual acuity gain in 8 of 10 patients²⁹.

We inject tPa (0.3-0.4 ml; 12.5 μ g/0.1 ml) to submacular space using 37-40 G cannula after completing vitrectomy. By using high amounts of fluid, we aim displacement of condensed retina and detachment of inferior retina in addition to lysis of subretinal hemorrhage by tPa. As such, we facilitate displacement of subretinal hemorrhage to inferior subretinal area. After achieving condensation and mobilization of clot, we apply fluid-air exchange.

We use SF6 gas for tamponade and position the patient to 45° head-position (reading head position) at least 3 days (Picture 2a,b,c,d).



Picture 2a,b,c,d. Pre- and post-operative fundus images of 2 patients who were treated with PPV plus tPa plus intravitreal gas with 45° head-position (reading position) In both patients, >3 lines VA gain was achieved and anti-VGEF therapy is continuing for choroidal neovascular membrane

It is difficult to determine toxicity of tPa given via subretinal route. Toxicity findings can be masked by removal of submacular clot. Toxicity findings such as exudative retinal detachment, RPE hyper-pigmentation and reduction in b wave in electroretinography can be observed in patients received tPa used high concentrations (>100 µg)³⁰. In previous studies, subretinal tPa dose ranged from 12 to 48 µg in general. No toxicity was reported following these tPa doses^{31,32}.

PPV plus tPa injection plus SF6 tamponade was found to be more effective than intravitreal tPa alone regarding visual outcomes. However, it requires specific surgical skills. In addition, it is associated with retinal detachment, cataract formation, endophthalmitis, choroidal neovascularization, cystoid macular edema, elevated IOP or hypotonia³⁴.

2.3. Macular Translocation

It is aimed to remove re-foveal neurosensory retina from dysfunctional RPE and re-position over intact RPE.

Total detachment is applied to retina using 36-41 G subretinal cannula. Detachment is started from equatorial region in general. It may be needed to give fluid from multiple sites. A few air-fluid exchanges can be needed to advance detachment to posterior. In patients with age-related macular degeneration, the most important and challenging step is to detach scarred and adhesive tissue under fovea. After achieving detachment, 360° peripheral retinotomy was performed and retina is stabilized partially by administering liquid perfluorocarbon. Retina is held and rotated by assistance of back-flush and fovea is re-

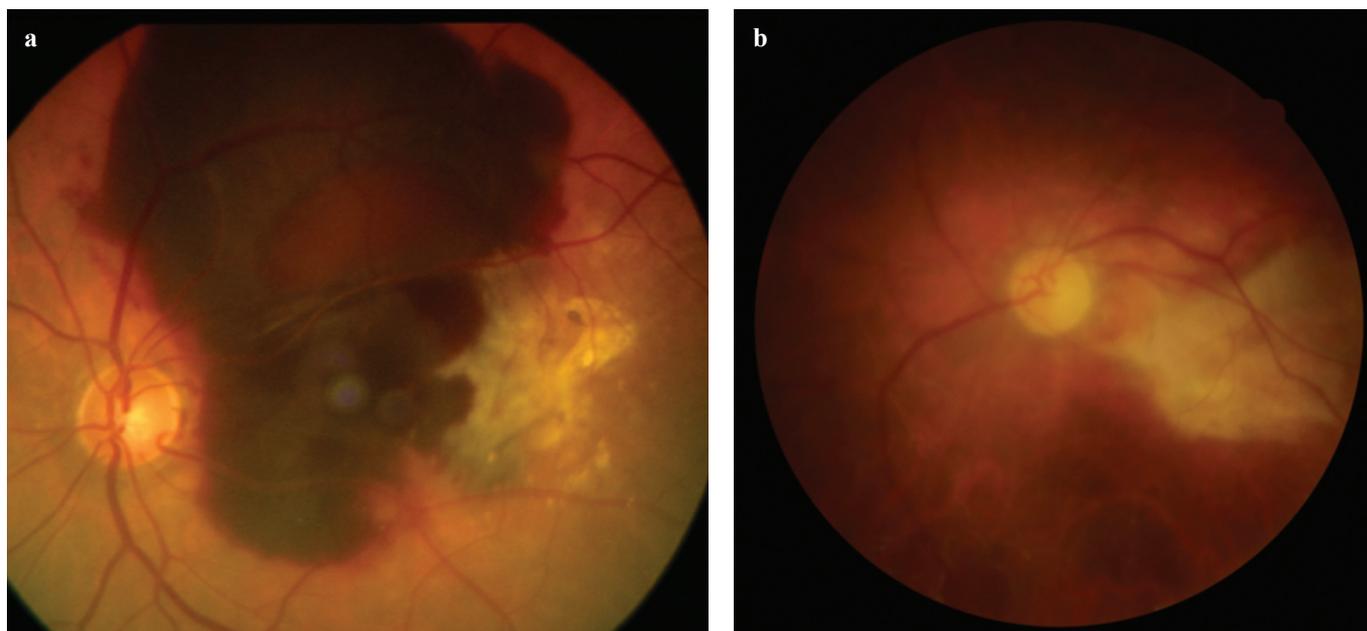
positioned over intact RPE. Then, vitreous is filled with liquid perfluorocarbon and retinal relief is achieved. 360° laser is applied and liquid perfluorocarbon-silicone oil exchange is performed (Picture 3a, b).

In a study on 3 patients with submacular hemorrhage secondary to age-related macular degeneration, Machemer et al., reported results of macular translocation. In PPV, fovea was rotated by subretinal infusion and 360° retinectomy in order to detach retina and fovea was displaced by 30-80° when compared to original location. By this technique, visual acuity was improved up to 20/80 in one patient while visual acuity was decreased due to PVR development in remaining 2 patients. In the study, preoperative submacular hemorrhage duration was not specified³⁵.

Wong et al. reported visual acuity gain in all of 29 patients with age-related macular degeneration after macular translocation.

It was reported that there was submacular hemorrhage in 6/29 patients and improvement in final visual acuity in all patient groups³⁶.

Abdel-Meguid et al. published a prospective study in which patients were followed over a year after macular translocation. In the study, there was submacular hemorrhage in 15 patients. All patients underwent surgery within 1 to 16 weeks. At year 1, ≥ 3 lines improvement in ETDRS was found in 14 patients while ≤ 3 lines visual acuity loss was detected in one patient. Mean visual acuity gain was 4.5 line at the end of 12-months follow-up.



Picture 3a,b: Pre- and post-operative fundus imaging in a patient who underwent macular translocation after PPV, subretinal neovascular membrane and removal of scar tissue.

Retinal detachment and PVR development was observed in one-third of patients³⁷.

Macular translocation is a therapeutic alternative that may provide positive outcomes in submacular hemorrhage. However, it may lead several complication choroidal neovascular membrane, choroidal hemorrhage or PVR development. Thus, such complications should be taken into account in decision-making process for surgery^{38,39}.

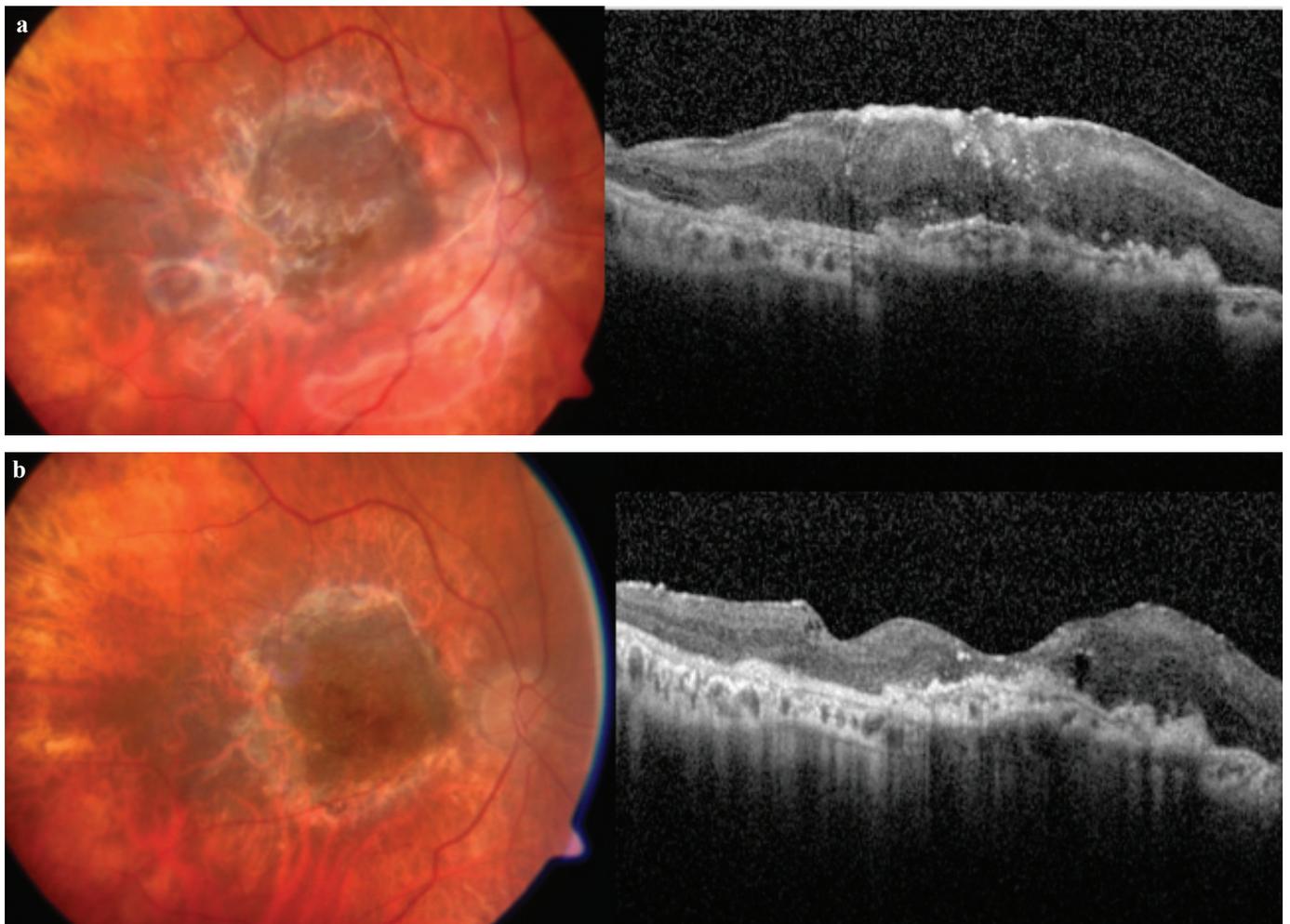
Based on our experiences, the most important issue is extent of hemorrhagic area. In preoperative evaluation, intact RPE region where fovea will be re-positioned should be well-defined and alternative techniques should be considered if high-degree rotation is needed.

2.4. RPE- Choroid Patch Graft

In this technique, either temporal retinal detachment up to 180° or complete retinal detachment by 360° can be performed. After detachment, retinal rotation is achieved by liquid perfluorocarbon administration;

thus, working area is exposed. Subretinal hemorrhage and scarred tissue are removed. Bleeding is controlled by cautery and laser photocoagulation in the area where RPE-choroid patch will be harvested. RPE-choroid patch incision is performed using scissors at margins marked by cautery and removed leaving bare sclera. The graft harvested is transferred beneath foveal centre under liquid perfluorocarbon. Subretinal perfluorocarbon is aspirated. Liquid perfluorocarbon is given over retina in order to achieve retinal relief. After laser on retinotomy region, liquid perfluorocarbon-silicone oil exchange is performed (Picture 4a,b) .

When it was shown that subretinal scar removal failed to achieve positive visual outcomes in the study by Bressler et al.⁴¹, Peyman et al. reported a case report in which autologous RPE-choroid graft was implanted to subretinal space after removal of subretinal scar. Authors reported that visual acuity was improved from finger count to 20/400 in their case⁴².



Picture 4a,b: Silicone oil removal and membrane peeling were performed in a patient developed epiretinal proliferation under silicone following RPE-choroidal patch graft. 1/01 central visual acuity was achieved.

In another study Bressler et al., surgical procedure was modified and RPE-choroid graft was harvested from paramacular region adjacent to implantation area. It was found that mean visual acuity was decreased from 20/132 to 20/289. In addition, severe complications such as retinal detachment and massive bleeding was reported in 8 of 12 patients, resulting in high rate of complication. The lack of improvement in visual acuity was attributed to RPE-choroid graft harvested from paramacular region where pathological changes may present.

Based on negative visual outcomes, the technique was modified where RPE-choroid graft is harvested from healthy mid-peripheral area in which cells are less commonly affected by disease. After removal of neovascular complex, RPE-Bruch membrane and full-thickness choroid graft was harvested from above-mentioned area and implanted beneath macula. This technique was employed in 15 patients in 3 different studies. It was seen that mean visual acuity was improved from 20/502 to 20/182^{44,45,46}.

Parolini et al. reported long-term outcomes in patients with atrophic and exudative maculopathy who were treated with RPE-choroid graft technique. In the study including 80 eyes of 84 patients, it was reported that mean visual acuity was improved from 20/320 to 20/200.

In 40% of eyes, there was at least 15 letters gain in final visual acuity.

RPE-choroid patch technique comprises an alternative to macular translocation. Torsional diplopia seen in patients with good visual acuity in contralateral eye in macular translocation is less commonly seen in RPE-choroid patch technique. However, vision can be decreased slightly in long-term follow-up after RPE-choroid graft. This can be explained by incomplete revascularization of RPE-patch graft and photoreceptor apoptosis induced by surgical manipulation²¹.

CONCLUSION

As reported in many studies, submacular hemorrhage due to age-related macular degeneration can result in severe, irreversible loss of vision^{2,4,15}.

Medical history and examination should be assessed carefully before establishing a treatment plan. Visual acuity before submacular hemorrhage, hemorrhage duration, contralateral eye, etiology, drug use which may cause hemorrhage and characteristics of hemorrhage (localization, thickness and extent) should be addressed.

In the treatment of submacular hemorrhage, several

techniques have been defined, including subretinal tPa, pneumatic displacement, intravitreal tPa plus pneumatic displacement, RPE-choroid patch graft and macular translocation. However, there is no consensus on optimal treatment of submacular hemorrhage.

In some studies, it was emphasized that shorter duration of submacular hemorrhage before surgery resulted in positive influence on final visual acuity^{18,19}. Also, there are studies suggesting that hemorrhage duration has no effect on prognosis^{17,27}. It was suggested that prognosis is worse in massive bleeding and hemorrhagic detachment of pigment epithelium⁴⁸.

Initially, intravitreal tPa plus anti-VEGF and pneumatic displacement can be recommended due to its feasibility and low complication rate when compared to vitrectomy. However, hemorrhage involving large areas and challenging cases, PPV plus tPa injection has more positive effects on visual outcomes. Vitrectomy allows complete clearance of submacular hemorrhage and is more appropriate for massive bleeding.

We think that tPa will not be sufficient in subretinal hemorrhage, thus, we performed macular translocation or RPE-choroid patch which are associated with higher risk.

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