Original Article

Comparison of platelet-rich plasma and inverted internal limiting membrane flap for the management of large macular holes: A pilot study

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Purpose: To compare the safety and efficacy of 25-gauge pars plana vitrectomy (PPV) with either platelet-rich plasma (PRP) or inverted internal limiting membrane (ILM) flap for the treatment of large macular hole. **Methods:** Pseudophakic patients with idiopathic macular holes with a minimum diameter (MD) of 600–1500 μm were randomized into two groups (30 patients each): 25-gauge PPV with either inverted ILM flap (group A) or PRP (group B). **Results:** Mean MD in groups A and B were 803.33 ± 120.65 μm and 784.73 ± 120.10 μm, respectively ($P = 0.552$). Mean base diameter in groups A and B was 1395.17 ± 240.57 μm and 1486.90 ± 281.61 μm, respectively ($P = 0.180$). The median presenting best-corrected visual acuity (BCVA) was logMAR 0.78 (range 0.78–1.00) and logMAR 0.78 (Range 0.60–1.00) in groups A and B, respectively ($P = 0.103$). Anatomical closure was achieved in 90% ($n = 27/30$) and 93.3% ($n = 28/30$) eyes in groups A and B, respectively ($P = 0.158$). Type 1 closure was achieved in 76.7% ($n = 23/30$) and 83.3% ($n = 25/30$) eyes in groups A and B, respectively. Median BCVA at postoperative 3-month in groups A and B was logMAR 0.60 (range 0.48–0.60) and logMAR 0.60 (range 0.48–0.78), respectively ($P = 0.312$). The average visual improvement was 2.0 and 2.5 early treatment diabetic retinopathy study (ETDRS) lines in groups A and B, respectively ($P = 0.339$). None of the patients developed postoperative exaggerated inflammatory reactions. **Conclusion:** Using platelets for the treatment of large macular holes is as safe and effective as an inverted ILM flap.

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Owing to its high success rates, macular hole (MH) surgeries are one of the favorite surgeries of the vitreoretinal surgeons.[1,2] However, a large MH still remains a surgical challenge as they are associated with the high risk of surgical failure and poor visual gain.[1-4] Chhablani *et al*. demonstrated that the predicted probability of type 1 closure was 100% only if the minimum diameter (MD) of hole is <300 μm, around 20–80% if MD is 600–900 μm, and only <20% if MD is >1000 μm.[2]

A number of techniques such as retina expansion technique, MH hydrodissection, arcuate retinotomy, and anterior lens capsular flap transplantation have been described for the treatment of large MHs.[5-8] Michalewska *et al*. described the inverted internal limiting membrane (ILM) flap technique, which changed the way large MHs are treated worldwide.[9] Several studies have proved that the surgical outcome of large MH is better with inverted ILM flap compared to conventional ILM peeling.[9-13]

Clinical practice throughout the world is now moving toward regenerative medicine.[14] One of the regenerative agents currently used is platelet-rich plasma (PRP), which releases high levels of growth factors and bioactive molecules in physiologic proportions. This hastens the natural healing process by enhancing directed cell migration, proliferation, and differentiation. It has been successfully utilized in the fields of plastic, cosmetic, reconstructive, oral, and orthopedic surgery.[15-17] Although the use of platelets for the treatment of MH has previously been reported, literature lacks studies comparing its efficiency with inverted ILM flap in large MH.[5,18-22]

We compared the safety and efficacy of 25-gauge pars plana vitrectomy (PPV) with either PRP or inverted ILM flap for the treatment of large MH.

Methods

This prospective study was done at a tertiary care eye hospital in south India from January 2017 to July 2018. Ethical clearance was obtained from the institute's review board (Registration No. ECR/182/Inst/TN/2013 dated 20/04/2013). The study adhered to the tenets of the declaration of Helsinki. All the surgeries were performed by a single vitreoretinal surgeon (NB).

Patients with idiopathic full-thickness macular hole (FTMH) with an MD of 600–1500 μm were included. All the patients were pseudophakic and had not undergone any prior

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vitreoretinal surgery. Patients with traumatic and myopic MH, MH-associated retinal detachment, axial length <22 mm or >24 mm, any coexisting ocular pathologies affecting vision, and patients refusing randomization were excluded. The patients were randomized into two groups with the help of system-generated random number. The size of the MH was not taken into consideration before randomization. The patients underwent 25-gauge PPV with either inverted ILM flap (IFT, group A) or PRP (group B). The nature of the surgery and the associated complications were explained to the patients and written consent was taken.

One week before the surgery, all the patients (both groups) underwent a medical examination by the physician. Their blood samples were tested for sugar levels, human immunodeficiency virus (HIV), and hepatitis B and C. Any patient with positive blood tests or any focus of infection in their body were excluded from the study.

Presenting best-corrected visual acuity (BCVA) was recorded and converted into logarithm of the minimum angle of resolution, that is, logMAR for statistical analysis. Spectral-domain optical coherence tomography (SD-OCT) using high definition 5-line raster scans and 3-dimensional 512×128 macular cube scans passing through the fovea was done and MH parameters were measured.[4]

PRP was prepared inside the operating room (OR). Just before the start of surgery, a 20 mL syringe was filled with 2 mL anticoagulant citrate dextrose solution A (ACD-A, Fresenius Medical Care, Bad Homburg, Germany). The ACDA-filled syringe was then filled with 18 mL of the patient's blood, taken from his anti-cubital vein with the help of a scalp vein. The 20 mL mixture was injected into Dr PRP Kit (Emergo Europe, Netherlands) through the upper part at a moderate speed so that neither the blood clots, due to slow speed, nor the cells get damaged due to rapid transit [Fig. 1a]. As the two compartments in the kit are intercommunicating, both compartments get filled.

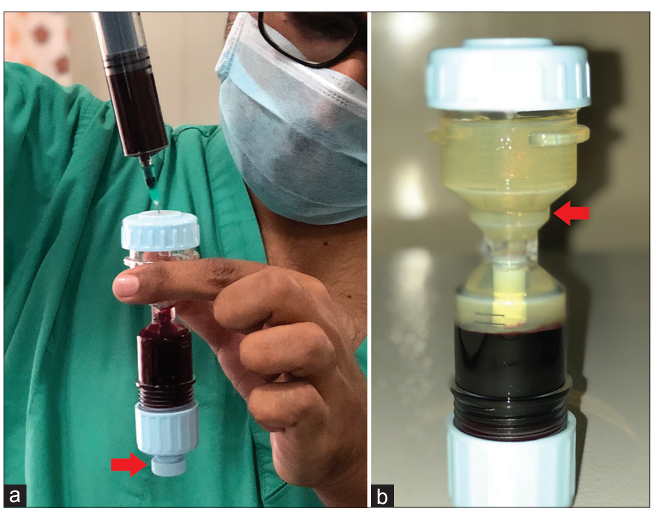

Figure 1: Preparation of platelet-rich plasma (PRP). (a) 20 mL syringe with a solution of 2 mL anticoagulant citrate dextrose solution A (ACD-A) and 18 mL of blood is injected into the Dr PRP Kit through the upper injection port. The kit has a knob that can be rotated to lock and permanently separate the upper and lower compartments (red arrow). (b) After the first centrifugation, the red blood cells settle in the lower compartment, while the plasma comes to the upper compartment (red arrow)

The tube was placed inside the REMI PRP centrifuge machine (REMI Group, India) for double-centrifugation. The first centrifugation took around 15 min and separated the plasma from red blood cells (RBCs). The RBCs being heavier, settled down in the lower compartment, while the plasma came to the upper compartment [Fig. 1b]. The two compartments were then locked by rotating the knob at the bottom of the tube. The tube was centrifuged again for 6 min to achieve platelet concentration. The platelets being heavier settled at the bottom of the upper compartment, while the platelet-poor plasma (PPP) came to the top. The PPP was taken out through the upper part and discarded. PRP was then collected and used within 30 min of preparation.

Patients in both groups underwent 25-gauge PPV. Vitreous was stained with triamcinolone acetate (Aurocort, Aurolab, India) to ensure its complete removal. ILM was stained with 0.05% brilliant blue G dye and peeled in a circular fashion for approximately 2-disc diameters around the hole.

In inverted ILM flap group, margins of the peeled ILM were left attached to the MH edges and trimmed to appropriate size. After performing fluid-air exchange (FAE), the ILM flap was tucked into the hole with diamond-dusted membrane scraper (DDMS; Synergetics, Inc., O'Fallon, MO, USA). Postoperative tamponade was provided with sulfur hexafluoride (SF6) gas with 2 weeks of prone positioning.

In the PRP group, ILM was peeled off. After performing FAE, few drops of PRP was injected directly over the MH, while the rest was sent for platelets count and microbiological examination. Postoperative tamponade was provided with SF6 gas in supine position so as to allow the platelets to settle down on macula.

Postoperative visits were scheduled at day 1, 2 weeks, 1 month, and 3 months. Frequent follow-ups were scheduled, in case of any complication. At each follow-up visit, BCVA, intraocular pressure (IOP), and SD-OCT were recorded. The outcome measures were anatomical and visual outcomes at

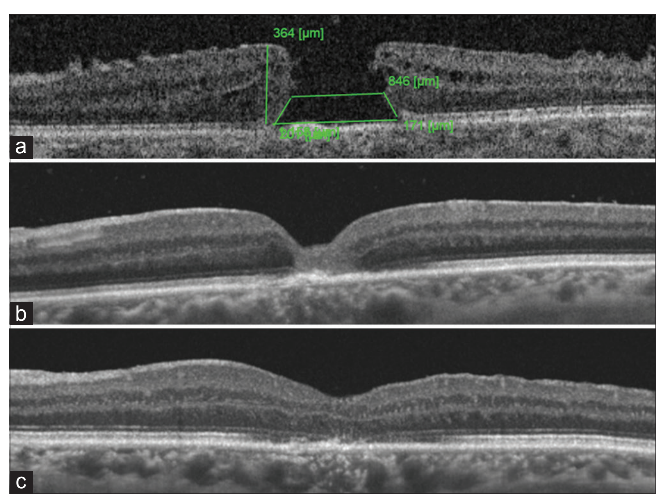

Figure 2: Ocular coherence tomography images of a patient treated with vitrectomy and platelet-rich plasma. (a) Preoperative configuration of macular hole; (b) 1 month after surgery; and (c) 3 months after surgery

the end of 3 months. The flattening of the hole with resolution of subretinal cuff of fluid was defined as anatomical closure. The flattening of MH with resolution of subretinal cuff of fluid and neurosensory retina (NSR) completely covering the fovea was termed as type 1 anatomical closure. When the whole rim of the NSR around the MH was attached to the underlying retinal pigment epithelium (RPE) but NSR was absent above the fovea, it was termed as type 2 anatomical closure.[23] When the hole was covered with only the flap without NSR it was called flap-only closure.[24]

Statistics

Statistical analysis was performed with STATA statistical software, Version 14.0 (StataCorp, College Station, Texas, USA). Continuous variables were expressed as mean (± standard deviation). The normality of the data was verified using histogram plot and Shapiro-Wilk test. Independent student's *t*-test, Mann-Whitney U test, or Wilcoxon sign rank test was used to find out the difference between two continuous variables. Chi-square test and Fisher's exact test were used to find out the difference between two noncontinuous variables. *P* value less than 0.05 was considered to be statistically significant.

Results

Sixty patients were randomized into two groups of 30 each. The mean age in groups A and B was 59.37 ± 6.71 and 64.33 ± 6.25 years, respectively ($P = 0.004$). The mean MD in groups A and B was 803.33 ± 120.65 µm and 784.73 ± 120.10 µm, respectively ($P = 0.552$). The mean base diameter (BD) in groups A and B was 1395.17 ± 240.57 µm and 1486.90 ± 281.61 µm, respectively ($P = 0.180$). The median presenting BCVA was logMAR 0.78 (range 0.78–1.00) and logMAR 0.78 (range 0.60–1.00) in groups A and B, respectively ($P = 0.103$) [Table 1].

Anatomical closure was achieved in 90% ($n = 27/30$) and 93.3% ($n = 28/30$) of eyes in groups A and B, respectively ($P = 0.158$). Type 1 closure was achieved in 76.7% ($n = 23/30$) of eyes in group A and 83.3% ($n = 25/30$) of eyes in group B [Fig. 2]. Four eyes (13.3%) in IFT group achieved flap-only closure while three eyes (10.0%) in PRP group achieved type 2 closure. Median BCVA 3-months post-surgery in groups A and B was logMAR 0.60 (range 0.48–0.60) and logMAR 0.60 (range 0.48–0.78), respectively ($P = 0.312$). The average improvement in BCVA 3-months post-surgery was 2.0 and 2.5 early treatment diabetic retinopathy study (ETDRS) lines in groups A and B, respectively ($P = 0.339$) [Table 2].

The three holes in the IFT group that failed to close had MD of 1007 µm, 986 µm, and 906 µm. The two holes in PRP group that failed to close had MD of 1201 µm and 939 µm. The four holes in the IFT group that had flap-only closure had MD of 1005 µm, 994 µm, 958 µm, and 896 µm. The three holes in the PRP group that achieved type 2 closure had MD of 772 µm, 786 µm, and 736 µm.

None of the patients in either group developed complications like hypotony, postoperative inflammatory reactions, endophthalmitis, or serous retinal detachment. No case of reopening of the hole was noted till the end of 3 months in either group. Microbiological culture of PRP solution was negative in all the cases.

Table 1: The baseline characteristics of the patients in the two groups

	Group A ILM inverted flap (IFT)	Group B Platelet-rich plasma (PRP)	*P*
Number	30	30	
Male:female	11:19	9:21	0.584[a]
Mean age	59.37±6.71 years (41.00-70.00 years)	64.33±6.25 years (45.00-75.00 years)	0.004[c]
Mean minimum diameter	803.33±120.65 µm (603.00-1007.00 µm)	784.73±120.10 µm (628.00-1201.00 µm)	0.552[c]
Mean base diameter	1395.17±240.57 µm (1005.00-1968.00 µm)	1486.90 µm±281.61 (905.00-2061.00 µm)	0.180[c]
Median baseline visual acuity	logMAR 0.78 (Snellen equivalent, 20/120) (range 0.78-1.00)	logMAR 0.78 (Snellen equivalent, 20/120) (range 0.60-1.00)	0.103[b]

ILM: Inverted limiting membrane, [a]Chi-square test, [b]Mann-Whitney U test, [c]independent *t*-test

Table 2: Anatomical and functional outcome of patients in both the groups

	Group A ILM inverted flap (IFT)	Group B Platelet-rich plasma (PRP)	*P*
Anatomical closure	90.0% (*n*=27/30)	93.3% (*n*=28/30)	0.158[b]
Type 1 closure	76.7% (*n*=23/30)	83.3% (*n*=25/30)	
Flap-only closure	13.3% (*n*=4/30)	-	
Type 2 closure	-	10.0% (*n*=3/30)	
No closure	10.0% (*n*=3/30)	6.7% (*n*=2/30)	
1-line improvement	20.0% (*n*=6/30)	53.3% (*n*=16/30)	0.007[a]
2-line improvement	16.7% (*n*=5/30)	10.0% (*n*=3/30)	0.706[b]
Median BCVA	logMAR 0.60 (Snellen equivalent, 20/80)	logMAR 0.60 (Snellen equivalent, 20/80)	0.312[c]
Average improvement (95% CI)	2.0 (1.2-2.8) ETDRS lines	2.5 (1.8-3.3) ETDRS lines	0.339[d]
BCVA ≥20/60	46.7% (*n*=14/30)	36.7% (*n*=11/30)	0.432[a]

BCVA: Best-corrected visual acuity, ETDRS: Early treatment diabetic retinopathy study. [a]Chi-square test, [b]Fisher's exact test, [c]Mann-Whitney U test, dindependent *t*-test. *P* value is less than 0.05 i.e. it is statistically significant

Discussion

Inverted ILM flap has now become the standard treatment of care for the management of large MHs throughout the world.[9-13] However, this technique is limited by its steep learning curve and difficulty in maintaining the flap during FAE. Modifications such as the use of viscoelastic cap, perfluorocarbon liquid (PFCL), autologous blood clot, and cabbage-leaf technique have been proposed to prevent flap dislocation.[25-31]

PRP is increasingly being used as regenerative medicine in other fields of medicine. However, studies evaluating the use of this "healing adjuvant" in MH surgery still remains rudimentary. Not many reports regarding the use of platelets for the treatment of MH exist. Paques *et al*., in their randomized control trial (RCT), reported that the anatomical success rate for primary MH was significantly greater in the group where platelets were used as an adjunct compared to vitrectomy alone group (98% vs 82%). However, the study being old had two major drawbacks, that is, OCT was not used to measure MH size and ILM peeling was not done.[21] Other studies have reported a primary closure rate of 95–100% with the use of platelets along with ILM peeling.[18-20,32] An anatomical closure rate of 78–85% has been reported with the use of autologous platelet concentrate (APC) during re-surgery in case of persistent MH.[22,33] Coca *et al*. reported successful anatomical closure of a single chronic traumatic MH with BD of 3000 μm.[34] However, most of the reports are either single-arm non-comparative studies or include small MHs. The efficiency of platelets for large macula holes is limited to mere case reports.

We compared the outcome of 25 G vitrectomy and inverted ILM flap with 25 G vitrectomy and PRP for the treatment of large MHs. Our results showed that the anatomical and visual outcomes of inverted ILM peeling with PRP and inverted ILM flap were similar. As a high concentration of platelets is achieved in PRP, a high concentration of growth factors such as epithelial growth factor, transforming growth factor, and the platelet-derived growth factor is added to the local milieu, which helps drive the regenerative mechanism.[15-17] Burmeister *et al*. in their *in vitro* studies have demonstrated that autologous platelet concentrate promotes better growth and migration of Muller cell compared to both control and serum. In fact, ILM peeling and platelets may have a synergistic action as ILM peeling stimulates reparative gliosis via muller cells activation, which is enhanced by platelets, too.[35]

Several safety concerns about the use of PRP have been raised. The most important concern is the increased chance of endophthalmitis. However, we did not encounter any case of endophthalmitis or culture growth in any of the PRP samples. The chances of infection were reduced by the use of specialized kits, which prevented exposure of contents to environment at any point in time. Also, PRP has been shown to have antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans*, and *Cryptococcus neoformans*.[17] The second concern is the presumed increased risk of inflammatory reaction to PRP. Gamulescu *et al*. reported a case of exudative retinal detachment after using APC for the treatment of MH.[36] However, none of the patients in our study developed out of proportion inflammation.

The benefits of other blood-based derivatives in MH surgery have also been studied earlier.[37,38] Banker *et al*. reported that serum may have a possible benefit in larger holes.[38] Ghosh *et al*. reported earlier and better visual rehabilitation with the use of whole blood. They attributed this to earlier photoreceptor regeneration and was confirmed by inner segment/outer segment junction continuity and increase in outer foveal thickness on OCT.[39,40] On the contrary, Purtskhvanidze *et al*. reported that while APC was effective in the treatment of persistent MH, autologous whole blood did not (85.2% vs 7.1%).[41]

To the best of our knowledge, this was the first prospective study comparing the efficacy of 25 G PPV and PRP with 25 G PPV and inverted ILM flap for treatment of large MH. In our pilot study, we found that the use of platelets for the treatment of large MH was not only safe but also equally effective to inverted ILM flap. With the availability of specific kits, PRP can now be prepared easily and safely in the OR itself. However, the patients should be screened carefully for a systemic disease like HIV, Hepatitis B and C, and with any other foci of infection. Although there is no data suggesting that the use of PRP for treatment of FTMH is contraindicated in such patients, it is better avoided. The possible increased risk of endophthalmitis and inflammation makes them less attractive for practicing ophthalmologists. Also, the additional cost burden and technical challenges associated with its preparation make it difficult to be copied on wide scale. Inverted ILM flap technique remains the preferred technique in such cases.

Conclusion

This study was limited by its small sample size and short duration of follow-up. As the ease of obtaining whole blood makes its use more repeatable in clinical practice, adding a third arm with whole blood will not be out of place. Although initial studies show that blood-based derivatives are safe and effective, it is necessary to carry out randomized clinical trials to evaluate the potential of whole blood as well as autologous platelets in MH surgery.

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Conflicts of interest

There are no conflicts of interest.

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