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Comparative Study of Myringoplasty with and without Autologous PRP in Large Central Perforation

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Abstract: ***Background: Myringoplasty operation is the reconstruction of the tympanic membrane (TM) which is performed to prevent recurrent discharge of the ear and to improve the hearing impairment which is caused by TM perforation. Platelets are the key factors in tissue repair mechanisms. They provide essential growth factors, which stimulate fibroblasts to create extracellular matrix deposition and neovascularization. Aim: This study aims to assess the efficacy of platelet rich plasma(PRP) in myringoplasty with respect to graft uptake and hearing outcome. Materials and Methods: A total of 88 patients diagnosed as COM mucosal inactive disease for more than 6 weeks having large size perforation were divided into groups of 44 each. Patients in group A who underwent myringoplasty with PRP while in second B underwent myringoplasty without PRP. Pre- and post-operative graft uptake and pure tone audiometry were performed for all the patients, and the outcomes were compared. Results: Both groups were statistically matched with regard to age and sex. At three months post-operatively, the success rate (graft uptake) in group A was significantly higher than in group B. The success in terms of graft uptake and hearing outcome was achieved in 40 patients in case group and 37 patients in control group. Conclusion: Topical autologous PRP application during myringoplasty is safe, can be easily prepared, highly efficient and successful with no reported complication. PRP not only enhances healing of chronic TM perforations but also avoids infection.***

Keywords: Myringoplasty, PRP, Graft uptake

1. Introduction

Myringoplasty is the operation in which the reconstructive process is limited to repairing a tympanic membrane perforation and there is no involvement of ossicular chain. The key objectives in the indication of a myringoplasty are: restoring the integrity of the tympanic membrane and improving hearing in the damaged ear [1].

Tympanic membrane graft migration due to natural events taking place in the reconstructed tympanic membrane can explain some in-situ failures and this remains a significant problem. It can be suggested that any substances that promote rapid and effectual growth could prevent graft migration because of their direct cohesion with the tympanic membrane [2].

There is a constant search for biomaterials that meet certain requirements, including being safe, biocompatible, low in cost and as structurally similar to human tissue as possible [3,4].Autologous platelet concentrates are widely being used in conditions that require rapid healing.Platelet Rich Plasma (PRP) is defined by a portion of plasma fraction of autologous blood having a platelet concentration above baseline with the full complement of clotting and growth factors like platelet derived growth factor, vascular endothelial growth factor and transforming growth factor. PRP serves as a growth factor agonist and has both chemotactic and mitogenic properties. It functions as a tissue sealant and an adhesive surgical hemostatic agent. PRP is biocompatible, inherently safe and free from transmissible diseases such as HIV and hepatitis. It accelerates the regeneration of endothelial, epithelial and epidermal layers. It also enhances collagen synthesis, angiogenesis and soft tissue healing and decreases dermal scarring by reversing glucocorticoids that mediate the inhibition of wound healing. [5,6,7,8,9] This study was undertaken to evaluate the efficacy of platelet rich plasma in underlay myringoplasty using temporalis fascia graft in cases of large size central perforation.

Aims and Objectives

Comparative study to assess the efficacy of platelet rich plasma in myringoplasty with respect to:

1) Graft uptake
2) Hearing outcome

2. Materials and Methods

This comparative and prospective study was conducted in the Department of ENT and Head Neck Surgery, Moti Lal Nehru Medical College, Swaroop Rani Nehru Hospital Prayagraj, UP from August 2020 to July 2021, after due clearance from Institutional Ethics Committee.

This study includes 88 patients of age group 20-40 years of age, irrespective of gender, who had diagnosed chronic otitis media mucosal inactive disease for more than 6 weeks having large size central perforation and PTA showing only conductive hearing loss.

Patients having sequelae or complications of chronic otitis media, discharging ear, acute mastoiditis in past, previous history of ear surgery, concomitant otitis externa and any tympanosclerotic patch, active focus found in nose, throat,

or oral cavity, PTA showing sensorineural or mixed hearing loss, bleeding disorders like thrombocytopenia, hemophilia, etc., patient on anticoagulant therapy, fibrinolytic therapy, or immunosuppressant therapy and Medical comorbidities like diabetes mellitus, hypertension, anemia, tuberculosis, autoimmune diseases, sepsis, unstable angina or malignancy were excluded from the study.

All patients were properly assessed, clinically by history taking, a general physical examination, oto-endoscopic examination, and examination under microscope. Audiological assessment was done by tuning fork test, pure tone audiometry, and radiological investigation such as X-ray mastoid (Schuller's view) or HRCT Temporal bone, if any indications. Patients, after a written informed consent, who fitted in our criteria were admitted, routine blood investigations (including coagulation profile) were done and were posted for surgery. All procedures were conducted under local anesthesia with or without sedation.

Total Patients (n=88) were divided into 2 groups depending on the procedure performed; Group A (N_1=44) patients underwent myringoplasty using temporalis fascia graft with PRP and in Group B (N_2=44) patients underwent myringoplasty using temporalis fascia graft without PRP.

PRP Preparation

The blood sample for PRP was taken from patients of Group A before the operative procedure. First, 10 ml venous blood of the patient was taken into a tube containing an Anticoagulant Citrate Dextrose-A (ACD-A) which avoids platelet activation and degranulation .The first centrifugation was a "soft spin"(2400 rpm for 10 mins), which separates blood into three layers, namely bottom-most layer containing RBC (55% of total volume), top most acellular layer called Platelet Poor Plasma- PPP (40% of total volume), and an intermediate Platelet Rich Plasma layer (5% of total volume) called the "Buffy coat". Using a syringe PPP, PRP and some RBCs were transferred into another tube without an anticoagulant. This tube underwent a second centrifugation; it was longer and faster than the first one, so called "hard spin"(3600 rpm for 15 mins). This allows the PRP to settle at the bottom of the tube with very few RBCs. The acellular plasma (80% of the volume) was found at the top. PPP was removed with a syringe and discarded and the remaining PRP was shaken well. At the time of application, PRP was first activated after combination of equal volume of a sterile saline solution containing 10% calcium chloride (a citrate inhibitor that allows the plasma to coagulate) and 100U/ml sterile thrombin (an activator that allows polymerization of the fibrin into an insoluble gel, which causes platelets to degranulate and release the mediators and cytokines), which results in gelling of this platelet concentrate.

Operative Procedure

In all the selected cases, myringoplasty with temporalis fascia graft via postaural approach was performed under local anesthesia with or without sedation. Temporalis fascia graft was placed lateral to handle of malleus. Tympanomeatal flap was reposited after making a bed of gelfoam in middle ear. In group A, The PRP was applied with a tuberculin syringe fitted with a needle, onto the graft visible through the perforation. Small pledgets of gelfoam soaked in PRP was used to overlap the junction of rim and graft circumference. Bismuth Iodoform Paraffin Paste (BIPP) and gelfoam packing was done while in group B, BIPP and gelfoam packing was done without application of PRP.

The results of group A and group B were compared utilizing Chi-square test for graft success rate and complications. An unpaired T-test was applied for comparison of hearing assessment of both groups. Statistical significance was accepted as $p<0.05$.

3. Observations and Results

Out of total 88 cases, most of the cases belong to the age group 20-24 year-46 cases (52.3%) followed by the age group 35-40 yr-19 cases (21.6%). Mean age of patients in group A was 27.68 ± 7.51 years (range 20 – 40 year) and in group B it was 25.82 ± 6.32 years (range 20 – 40 year).

The overall proportion of females & males in the study was 73.9%(65): 26.1%(23) while in group A this proportion was 70.5%(31) : 29.5%(13) and in group B the proportion was 77.3%(34) : 22.7% (10).

Out of 88 cases, the overall proportion of Bilateral COM mucosal disease, Left COM mucosal disease and Right COM mucosal disease was 37.5%, 27.3% and 35.2% respectively. In group A, this proportion was 18.2%, 31.8% and 50% respectively while in group B the proportion was 56.8%, 22.7% and 20.5% respectively. A greater proportion of Bilateral COM mucosal disease was present in control group

Graft Uptake Status

Table I: Distribution of Cases according to Graft Uptake Status in both groups (n=88)

Graft Uptake Status	Group A (N_1=44)		Group B (N_2=44)		Total		Chi square	p value
	No.	%	No.	%	No.	%		
Failed	4	9.1%	7	15.9%	11	12.5%	0.94	0.334
Success	40	90.9%	37	84.1%	77	87.5%		
Total	44	100.0%	44	100.0%	88	100.0%		

In group A(N_1=44), successful graft uptake was observed in 40 (90.9%) cases while in remaining 4 (9.1%) cases, graft failure occurred. On the other hand, in group B(N_2=44) successful graft uptake was observed in 37 (84.1%) cases while in remaining 7 (15.9%) cases, failure occurred. No significant difference was found in graft uptake ratio in group A and group B(p=0.334).

Hearing assessment

Hearing assessment has been studied in table no II and III.

Table II: Intergroup and Intragroup Comparison of Air Conduction (AC) in both groups (n=88)

Air Conduction (AC)	Group A(N_1=44)		Group B(N_2=44)		Unpaired t-test	
	Mean AC (in dB)	SD	Mean AC (in dB)	SD	t-value	p-value
Pre- Operative	41.98	9.54	42.27	12.10	-0.13	0.899
Post-Operative at 3 Months	26.48	9.08	30.25	11.89	-1.67	0.098
Intragroup	t=15.35, p<0.001		t=13.22, p<0.001			

In pre-operative cases, in group A,the mean AC was 41.98±9.54 (mean ±SD) while in group B mean AC was 42.27±12.10(mean±SD). No significant difference was observed in the mean air conduction threshold between group A and group B (p=0.899).

At post-operative 3rd month, in group A, the mean AC was 26.48±9.08(mean ±SD) while in group B mean AC was 30.25±11.89(mean ±SD). No significant difference was observed in mean AC between group A and group B (p=0.098).

The intragroup comparison showed significant changes in AC in group A(p<0.001) and group B (p<0.001) both.

On comparing the changes in mean AC between pre-operative and at three months postoperative time, the change in mean AC in group A was 15.50±6.70 (mean change ±SD) while in group B this change was 12.02±6.03 (mean change ±SD). The significant difference was found in AC change between group A and group B (p=0.012).

In group A, the mean ABG change was 11.93±5.54 (mean change ±SD) while in group B, the mean ABG change was 11.14±6.29 (mean change ±SD). No significant difference was found in ABG change between group A and group B (p=0.531).

Table III: Intergroup Comparison of Mean Hearing Improvement in both groups (n=88)

Hearing Improvement (Change)	Group A (N_1=44)		Group B (N_2=44)		Unpaired t test	
	Mean Improvement (in dB)	SD	Mean Improvement (in dB)	SD	t-value	p-value
Air Conduction (AC)	15.50	6.70	12.02	6.03	2.56	0.012
Air Bone Gap (ABG)	11.93	5.54	11.14	6.29	0.63	0.531

Complications

Various complications and their comparison in group A and B have been studied in Table IV.

In Group A, medialization of graft, residual pinpoint perforation and residual small size perforation were present in proportion 2.3%, (1), 2.3% (1) and 6.8% (3) respectively.

In Group B, medialization of graft, residual large size perforation and residual small size perforation were present in proportion 2.3% (1), 4.5% (2), and 11.4% (5) respectively. Residual small size perforation as a complication was most common amongst both the groups.

No significant difference was found in the proportion of various complications between group A and group B (p=0.460).

Table IV: Intergroup Comparison of Complications in both groups (n=88)

Complications	Group A (N_1=44)		Group B (N_2=44)		Total		Chi- square*	p-value
	No.	%	No.	%	No.	%		
Medialization of graft	1	2.3%	1	2.3%	2	2.3%	0.361	0.5479
Residual Large size perforation	0	0.0%	2	4.5%	2	2.3%		
Residual pinpoint perforation	1	2.3%	0	0.0%	1	1.1%		
Residual small size perforation	3	6.8%	5	11.4%	8	9.1%		
None	39	88.6%	36	81.8%	75	85.2%		
Total	44	100.0%	44	100.0%	88	100.0%		
** Chi square with Yates Correction two tailed test.*								

4. Discussion

Myringoplasty is an established and rewarding procedure done routinely by the ENT surgeons all over the world. There is an ongoing quest to improve the success rate, hearing improvement and reduce complications in myringoplasty surgery. When the otological procedures that involve tympanic membrane perforations are done, biomaterials or biological tissues are normally used as grafts.

In the previous years, there have been several attempts to use tissue adhesives in ENT surgeries. Thus, graft uptake could be facilitated by using substances that promote fast and effective growth by direct cohesion with tympanic membrane remnants. In our current study, we have used platelet-rich plasma (PRP) that has inherent ability to accelerate natural healing of the patient and is inherently safe. PRP is a growth factor carrier that promotes epidermal, epithelial, and endothelial regeneration, collagen production, soft tissue healing, and angiogenesis.[10] The autologous PRP is simple and easy to prepare with no reported side effects till now. In our study, as patient's own temporalis fascia graft was used and PRP was prepared from autologous blood in strict aseptic conditions, there was no potential risk of graft host reactions or any allergic reactions.

In our study we have included only large size perforations, this is unique because most of the studies have included all type of perforations in their study. Only a few studies have

been done only on large size perforation like **M.K Taneja**[11] and **M. Waheed el-Anwar *et al***[12] who have done study in large size perforation.

In our current study, the success rate in terms of graft uptake was found to be **90.9%** in Group A and **84.1 %** in Group B. Residual perforations were found in 4 cases; 1 case had pin-point residual perforation and 3 cases had small size residual perforations. In Group B out of 7 failures; 2 had large size residual perforation and 5 had small size residual perforation. The most common cause of failure in control group was found to be infection. This can also conclude that PRP prevents infection.

Among all platelet concentrates, platelet-rich plasma has been extensively studied. In otology, it is used for traumatic tympanic membrane perforation[13], type 1 tympanoplasty, for facial nerve regeneration, etc. A novel study done to assess the biostimulation effect of platelet-rich plasma on type 1 tympanoplasty studied by **Navarrete Álvaro *et al***[14]showed that platelet-rich plasma stimulates fibroblast and thus, aids in the closure of tympanic membrane perforations.

A study done by **Sankaranarayanan *et al***[15]on platelet-rich plasma-assisted tympanoplasty found that closure rates were better in patients in whom platelet-rich plasma was used, as compared with the control group. They assessed 25 patients in each group and found a closure rate of 92% in the study group and 70% in the control group. Our study is comparable with this study.

A study on myringoplasty with PRP done only on large size perforation done by **M.K. Taneja**[16] on 82 patients has graft success rate of 95.1% in case group and 85.3% in control, which is comparable with our study. This further confirms addition of PRP in myringoplasty enhances graft success rate.

A study done **by Disha Sharma *et al***[17] on 100 patients has an overall graft success rate in 92% in case group but in large size perforation, 80% graft uptake success rate was obtained. However, **M Waheed el Anwar *et al***[12] showed graft taken up in all cases of large central perforation with 100% success rate. The following results show that our study is in accordance with and is comparable with the previous studies.

A systematic search was conducted by **Juntao Huang *et al***[18] to screen the Medline, Embase, Cochrane, Scopus, and Web of Science databases up to July 2020. The studies were identified in accordance with the selection criteria by two co-authors independently. In this review, the average closure rate in the PRP case groups was 93.4%, compared to 78.6% in the control groups with conventional surgery alone. Our study is comparable with this study which has 90.9% success rate in terms of graft uptake.

We have also assessed hearing improvement at three months by pure tone audiometry (PTA). The hearing gain (at least 10 dB in air conduction) was obtained in **90.9%** in Group A and **63.6%** in Group B which was found to be statistically significant. The study done by **M.K.Taneja**[11] showed the hearing improvement of 78% in the case group and 46.3% in the control group and up to 95% in case group and 70% in control group in **M Kamel el Awady *et al***[19]study. However, analysis done by **Juntao Huang *et al*** [18] shows no significant differences in hearing results between case and group group.

In our study, the mean hearing gain in Group A was11.93$\pm$5.54 dB and in the Group B was 11.14$\pm$6.29 dB, which is statistically not significant. Theprevious studies showed the mean hearing gain in the case group from 9.08$\pm$3.33 in **S.Kutuk*et al***[20] up to 18.62 dB as in **SPS Yadav et al**. [4] Thus, we can conclude that the PRP may have additional improvement in hearing as compared to control group.

In our study, both Group A and Group B have one case each of medialization of graft. The reduced failures in the case group due to infection may suggest the antimicrobial effect of platelet rich plasma, however further studies are needed to support this fact. The platelet-rich plasma accelerates the healing of tympanic membrane perforation following myringoplasty. It prevents graft displacement or shrinkage, especially in wet grafts, with its sealant property. Platelet-rich plasma improves the overall success rate of myringoplasty. Furthermore, it has no noticeable side effects.[21]

Considering the higher success rate of myringoplasty with PRP as comparedto myringoplasty without PRP, without any noticeable side effects, we recommend that myringoplasty with autologous PRP should be preferred as it accelerates the tympanic membrane closure and prevent graft displacement.

5. Conclusion

Topical autologous PRP application during myringoplasty is safe, can be easily prepared, highly efficient and successful with no reported complication. PRP not only enhances healing of chronic TM perforations but also avoids infection.

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