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RESEARCH ARTICLE

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Comparative Evaluation of Efficacy of Antibiotics incorporated Platelet Rich Fibrin Versus Platelet Rich Fibrin alone in the Treatment of Intrabony Defects

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ABSTRACT

Background: Platelet rich fibrin (PRF) is regarded as second generation platelet concentrate which is widely used to treat intraosseous defects. Bacterial contamination in periodontal regeneration is prevented by systemic antibiotics which may give rise to drug resistance and other side effects. **Aim:** The study aimed to explore clinical and radiographic effectiveness of amoxicillin incorporated PRF in the management of intrabony defects. **Methods:** Sixteen intrabony defects were treated with either Amoxicillin incorporated PRF (test site) or PRF alone (control site). Clinical parameters such as probing pocket depth (PPD), relative attachment level (RAL) and relative gingival margin level (RGML) were recorded at baseline and 6 months post-operatively. Wound healing index (WHI) was assessed at 7 and 14 days post-operatively. The defect fill at baseline and 6 months was calculated using cone beam computed tomography (CBCT). **Results:** On intergroup comparison of mean PPD, RAL and RGML showed no statistically significant difference. Comparison of WHI between control group and test group showed significant healing at 7 days post-operatively. Defect fill change showed no significant difference between control and test groups from baseline to 6 months. **Conclusion:** Both the groups seem to be effective in the treatment of intrabony defects. Initial wound healing was better in test group. However, randomized controlled trials with larger sample size are required to evaluate the efficacy of amoxicillin incorporated PRF in periodontal regeneration.

Keywords: Platelet rich fibrin, intrabony defects, antibiotics, amoxicillin

INTRODUCTION

Periodontal therapy aims at treating the infection caused by pathogenic bacterial biofilm, arresting the progression of disease and reconstituting the structures of the periodontium that are lost, ultimately preventing tooth loss. Ideally, treatment of osseous lesions should result not only in probing depth reduction and clinical attachment gain, but also radiographic bone fill and closure of the defect via periodontal regenerative treatment.

Endogenous regenerative technology (ERT) can activate the host's innate capacity for regeneration and has recently gained attention in the field of regeneration.[1] Approaches to accelerate the clinical application of ERT include the use of autologous bioactive agents and therapeutic biomaterials.

According to Choukroun (2001), Platelet rich fibrin (PRF) is a second-generation autologous platelet concentrate is an autologous leukocyte and biomaterial.[2] It enables to obtain fibrin membranes that are abundant in platelets and growth factors, has a three-dimensional fibrin architecture that acts as a scaffold to maintain growth factors and does not rapidly disintegrate in the hours after its application.[3] PRF application in the treatment of intrabony defects has demonstrated substantial clinical advantages as well as improved periodontal defect bone fill as it contains platelet derived growth factors, Transforming growth factor-beta (TGF- β); Vascular endothelial growth factor (VEGF), Epidermal growth factor (EGF) and Insulin-like growth factor (IGF-1) slowly released over time and may prolong up to 28 days when it is used as a membrane for periodontal defects. Therefore, PRF can be used both as a grafting material and as a membrane to cover the grafting material.[4]

Studies have demonstrated that guided tissue regeneration (GTR) membrane as one of the successful method for periodontal regeneration but it is prone to bacterial contamination which affects the periodontal regeneration. Post-operative infection has a major role on effect of the surgical outcome. Prevention of bacterial contamination is done by systemic antibiotics. But it may give rise to drug resistance as well as side effects. In vitro studies showed that certain drugs like amoxicillin, tetracycline, etc. incorporated in GTR membrane prevents bacterial colonization. In this context, David Polak et al[5]showed in an in vitro study that incorporation of antibiotics like Penicillin, Clindamycin and Metronidazole in PRF exhibited long term antibacterial effect against Fusobacterium nucleatum and staphylococcus aureus. In addition to PRF's advantageous healing properties, risk of post-operative infection may be reduced using the modified PRF preparation.

According to our knowledge, there is no literature available regarding the use of Amoxicillin incorporated PRF in reducing the risk of post-operative infection and for the prevention of bacterial contamination of the membrane. Since, Amoxicillin is most widely used by dental practitioners because beta lactam antibiotics have a bactericidal effect against gram positive and gram negative microorganisms. Hence, this study compared and evaluated the clinical and radiographic effectiveness of amoxicillin incorporated PRF versus PRF alone in the treatment of intrabony defects.

MATERIALS AND METHODS

Study design

The present study was done at the Department of Periodontology, Dr. D. Y. Patil Dental College & Hospital, Pimpri, Pune, and was designed as a prospective randomized controlled trial (RCT) with a duration of 6 months. The clinical study protocol was approved by scientific and ethical committee of the institution.

Study population

Eight patients with moderate to chronic periodontitis who were systemically healthy were enrolled in the study. The enrolled patients had to meet the following requirements:

- Patients showing contralateral sites with $\geq$ 5 mm clinical probing pocket depth following phase 1 therapy
- Presence of interproximal intrabony defects with a depth of >3mm and radiographic evidence of periodontal osseous defects ;
- Involved teeth were vital and asymptomatic;
- Patients who agreed to give informed consent and willing to undergo the treatment;
- Patients with acceptable oral hygiene before receiving surgical therapy.

The exclusion criteria listed below were applied:

- Patients with aggressive periodontitis
- Pregnant and/or lactating women;
- Smokers;
- Patients with abnormal blood picture;
- Presence of gingival recession at surgical site;
- Patients allergic to Amoxicillin.

Randomization

Using a coin-toss method, the chosen sites were split into control and test sites randomly. The control sites received access flap with PRF alone, whereas test sites received access flap with Amoxicillin incorporated PRF.

Presurgical Therapy

Prior to surgery, each patient was given comprehensive advice on proper oral hygiene practices. A full-mouth supragingival and subgingival scaling and root planning (SRP) procedure were performed. A periodontal reevaluation was performed after 4 to 6 weeks of phase I therapy to confirm the study sites.

Clinical and radiographic measurements

The site specific plaque index (PI) [6], modified sulcus bleeding index (mSBI)[7], probing pocket depth (PPD) measured from gingival margin (GM) to the base of pocket, relative attachment level (RAL) measured from the lower border of the acrylic stent to the base of pocket, and relative gingival margin level (RGML) measured from the lower border of acrylic stent to the GM were clinical parameters that were recorded prior to surgery. To ensure reproducible placement of the periodontal probe, a specially designed acrylic stent with a groove was used. At 7 and 14 days following surgery, the surgically treated sites were assessed using the wound healing index (WHI)[8].

All IBDs were assessed at baseline and 6 months after surgery. For, all selected sites, CBCT scans were taken and the defects were seen in axial, coronal and sagittal sections which were acquired by imaging software.

Preparation of PRF

According to the protocol developed by Choukroun et al[2], the PRF was prepared. Just prior to surgery, 10 ml sterile tubes without anticoagulant were used to collect intravenous blood from the ante cubital vein. The tubes were immediately centrifuged for ten minutes at 3000 revolutions per minute. The PRF clot was separated from the other two layers by using sterile scissor and tweezer (acellular plasma and red blood cells). One part of the PRF was used as a grafting material and other part was prepared in the form of membrane obtained by placing it in PRF box and squeezing out fluid from the fibrin clot.

Preparation of Amoxicillin solution

Amoxicillin solution was prepared in the concentration of 20µg/ml. 500mg of amoxicillin capsule was dissolved in 100ml of distilled water to dilute the solution at a concentration of 5mg/ml (5000µg in 1000µl of distilled water). From this diluted solution, 4µl of solution was pipetted out. Further, this 4µl of solution was then diluted again by adding 996µl to make up a concentration of 20µg/ml. 20µg/ml concentration of freshly prepared Amoxicillin solution was injected to the blood using a syringe before centrifugation.

Surgical Procedure

A pre-procedural rinse of 0.2% chlorhexidine gluconate was used to ensure intraoral antisepsis, and to ensure additional oral antisepsis, povidone- iodine solution was used. Following the administration of local anesthetic, mucoperiosteal flap was reflected after the buccal and lingual/ palatal crevicular incisions were made. To get optimum access, the flap was extended both mesially and distally. Interproximal soft tissue was preserved as much as possible with care. Using area- specific curettes and ultrasonic instruments, meticulous defect debridement and root planning was carried. No osseous contouring was done. During the latter part of surgery, PRF was prepared. However, in the test site, freshly prepared Amoxicillin solution was injected to the blood prior to the centrifugation. In both test and control site, pre grafting suture was done. One portion of PRF as plug was placed in intrabony defect and care was taken not to overfill the defect. An additional PRF component was utilised as a GTR membrane to cover the defect. A 4-0 non-resorbable mersilk suture was used to reposition the mucoperiosteal flap and secure it in place. After the vertical mattress sutures were positioned, the surgical site was covered using periodontal dressing.

Postoperative Care

Analgesic (paracetamol 500 mg SOS) was prescribed along with Chlorhexidine 0.2% rinses twice daily for 14 days. Antibiotic (Capsule Amoxicillin 500 mg) was prescribed only in the control site. All individuals were given postsurgical instructions and the importance of oral hygiene maintenance was reinforced. After 7 days, periodontal dressing was removed for the assessment of WHI in both the groups. For the next one week, new dressing was given. After 14 days, the patients were recalled for removal of suture and assessment of WHI.

Post-Surgical Measurements

After 6 months post-surgery, soft tissue and hard tissue evaluations were performed. With previously used acrylic stents, soft tissue measurements were repeated. A second CBCT scan was done for the hard tissue reevaluation, and at 6 months the IBD measurement was reevaluated.

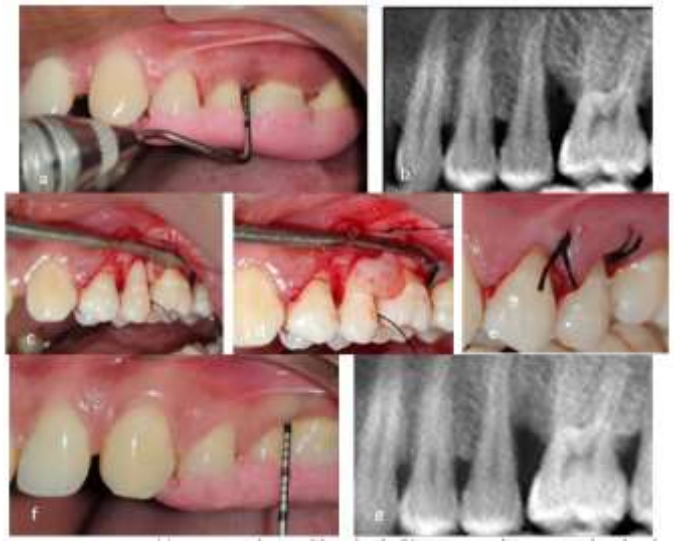

Figure 1: Control site (a) Pre-operative probing depth (b) pre-operative CBCT showing intrabony defect (c) placement of PRF plug (d) placement of PRF membrane (e) Primary closure of the defect (f) 6 months post-operative probing depth (g) 6 months post-operative CBCT showing defect fill

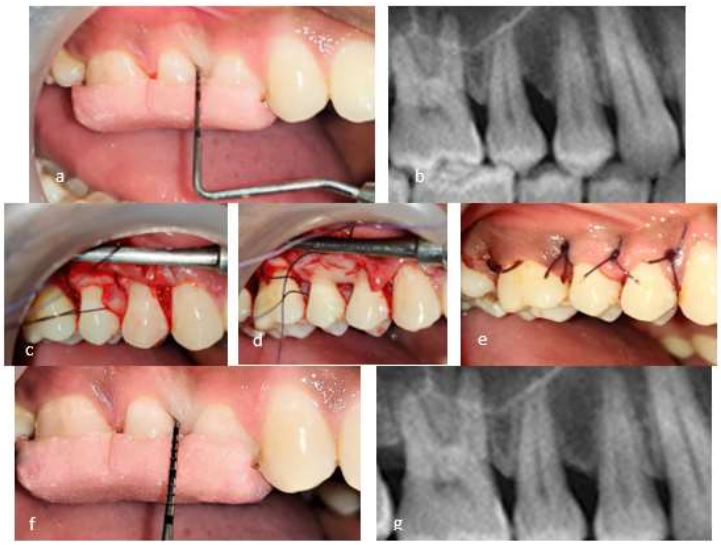

Figure 2: Test site (a) Pre-operative probing depth (b) pre-operative CBCT showing intrabony defect (c) placement of Amoxicillin incorporated PRF plug (d) placement of Amoxicillin incorporated PRF membrane (e) Primary closure of the defect (f) 6 months post-operative probing depth (g) 6 months post-operative CBCT showing defect fill

Statistical analysis

Data were analyzed using statistical software. Data was obtained and entered into Microsoft Excel Version 23. The data was entered into IBM Statistical packages for social sciences (SPSS) version 21 for statistical analysis. Frequency analysis of the categorical data and descriptive statistics for continuous data was performed. Mean and standard deviation was obtained for continuous variables. Paired t test was performed to compare the continuous variable at two different time period. Unpaired t test was performed to compare between two groups. Mann Whitney U test was performed to compare the nominal data between the groups and Wilcoxon sign rank test to compare nominal data in same group at two different time period. All the data assessed by keeping the confidence interval at 95% ($p<0.05$) obtained in the results were considered to be statistically significant

RESULTS

All 8 patients (16 sites) completed the study and wound healing was uneventful at baseline and 6 months. A statistically significant reduction in PI and mSBI was observed in both test and control sites at 6 months post-operatively ($P<0.001$) (Table 1). Comparison of mean SBI score between control group and test group was not statistically significant ($p>0.382$) (Table 2). Intergroup comparison of clinical and radiographic parameters at baseline and 6 months post operatively showed no statistically significant difference. A statistically significant improvement was observed in both sites in terms of PPD, RAL and IBD depth but not in terms with RGML in both control and test sites at 6 months post operatively (Table 3). No statistically significant difference was observed on intergroup comparison in terms of PPD, RAL, RGML and IBD at 6 months post operatively (Table 4). Comparison of WHI between control site and test site at 7 days showed statistically significant difference ($p<0.045$) but it was statistically insignificant at 14 days ($p>0.149$) (Table 5).

DISCUSSION

Second-generation platelet concentrate, platelet rich fibrin (PRF), a fibrin matrix in which platelets, cytokines and cells are entrapped and are released after certain time and serves as a sole grafting material as well as resorbable membrane. Post-operative infection is always a risk for wound healing. Bacteria can infiltrate and colonize the underlining wound tissues which causes loss of tissue integrity in the surgical site along with impaired healing.

Usually systemic antibiotics are prescribed to prevent the formation of microabscesses following GTR treatment and to prevent membrane contamination and consequent infection after the membrane exposure. But, systemic administration of antibiotics can give rise to drug resistance as well as some adverse effects. However, topical application of antibiotics is more effective than systemic use in preventing bacterial contamination of the membrane in periodontal regeneration.

In vitro study by Hung et al[9] and Cheng et al[10] demonstrated that incorporation of Amoxicillin or Tetracycline into GTR membrane reduced the adhesion of S. mutans or A.actinomycetemcomitans on the ePTFE, glycolide fiber, or collagen membrane for periodontal regeneration therapy. Cieslik-Bielecka et al[11] demonstrated that producing platelet rich gel 30 minutes after intravenous administration of amoxicillin and clavulanic acid (Augmentin) resulted in the gel having strong antibacterial activity against Enterococcus faecalis. It was suggested that it would be ideal to combine antibiotics with the PRF rather than administering them systemically. Also, in an in vitro study by David Polak et al[5] showed that PRF incorporated with antibiotics such as Metronidazole, Clindamycin, Penicillin showed long term antibacterial effect against F. nucleatum and S. Aureus. It provides the clinician to control post-operative infection promotes tissue healing and prevent local infection by reducing the need for systemic antibiotic regimen.

Till now, to the best of our knowledge there is no literature available regarding the use of Amoxicillin incorporated PRF in reducing the risk of post-operative infection and for the prevention of bacterial contamination of the membrane. Hence, this study was carried out to evaluate and compare the efficacy of amoxicillin incorporated PRF versus PRF alone for the management of intrabony defects.

In present study, Amoxicillin was used as antibiotic because it is said to be highly effective in reducing the post-operative bacteremia in a periodontal flap surgery and also prevents possible sequelae. Amoxicillin was most frequently prescribed to prevent post-operative infection as it can prove to be effective against gram positive and gram negative bacteria. In addition to being a desirable outcome of periodontal regenerative procedures, PD reduction may also be the most crucial clinical parameter as it directly affects the clinician's ability to instrument a treated region during follow-up visits. Also, RAL gain is an important clinical outcome in periodontal regeneration. The results of the this study are in accordance with the study by Pradeep AR et al.[12] Reduction in PPD and CAL gain might have been the result of true periodontal regeneration via new attachment in the case of PRF. After periodontal therapy, reduction in PPD is due to the combination of gain in attachment and gingival recession. Hence, it is important to assess the amount of gingival recession.

Healing by primary intention, in particular, refers to primary wound closure in which the flap margins are placed and held in direct contact until merged by tissue healing. In this study, an interesting finding is the WHI in test site. WHI was assessed at 7 and 14 days post-operatively. In control site, at 7 days, 50% of sites showed WHI score of 1 and the remaining 50% of sites showed slight gingival edema. Whereas in test site, 87.50% of sites showed WHI score of 1 and the remaining 12.5% of sites showed slight gingival edema. This difference between control and test sites was statistically significant ($p<0.045$). At 14 days, 87.50% of sites showed WHI score of 1 in control site and 12.5% (1 patient) showed slight gingival edema due to tissue tear in the area of gingival margin during the reflection of full thickness mucoperiosteal flap. Whereas, in the test site, 100% of the sites (8 patients) showed WHI score of 1. However, this difference between control site and test site was not statistically significant. At 7 days WHI was statistically significant in test site compared to control site. According to the study by Cheng et al[10] showed that incorporation of Amoxicillin into GTR membrane greatly reduced the bacterial adhesion after 48 hours of incubation. Additionally, Polak D. et al. in an in vitro study demonstrated significant inhibition of both aerobic and anaerobic growth compared to PRF alone and demonstrated antibacterial activity of PRF on incorporating antibiotics such as Clindamycin and Penicillin following incubation up to 4 days post preparation. These results confirm that Amoxicillin incorporated PRF preserve their antibacterial activity necessary for initial wound healing and suggesting the post-surgical slow release of antibacterial agent. In the present study, all hard tissue changes were assessed and measured by CBCT at baseline and after six months. Post-operatively, the CBCT provided best quality 3-dimensional images for evaluation of the morphology of the periodontal defects.

In both the control and the test sites, the average distance from the CEJ to the alveolar crest was 0.237+0.194 mm and 0.275+0.057 mm, respectively, suggesting slight gain from baseline to six months that was not statistically significant. At 6 months, there was no statistically significant difference in the alveolar crest levels between the control and test groups ($p> 0.887$). The distance from the crest of the alveolar bone to the base of the defect was used to determine the depth of the defect. Both crestal resorption and defect filling at the base of defect are possible methods of defect resolution. In control and test sites, the mean of defect resolution from baseline to 6 months was 1.937+0.086 mm and 2.3+0.027 mm which was statistically significant ($p<0.00$; $p<0.00$). However, the comparison of defect resolution between control and test sites at 6 months was not statistically significant ($p> 0.533$). These findings are consistent with a study by Sharma et al (2011)[13] showed significantly greater defect depth reduction in the sites treated with PRP and PRF as compared to the sites treated with open flap debridement.

The defect fill was measured from CEJ to the base of the defect with the CEJ serving as the fixed reference point. The mean defect fill from baseline to 6 months was statistically significant in both control and test sites. At 6 months, there was no statistically significant difference in defect fill between control and test sites ($p> 0.726$). These results are in accordance with Thorat et al (2011)[14] and Pradeep AR et al (2012)[12] which showed greater percentage of bone fill in the sites treated with PRF in comparison with sites treated conventionally. The study supports the significance and advantages of growth factors that are present in the PRF which accelerates the soft and hard tissue healing. High number of leukocytes concentrated in one region of the clot, with a specific slow release of growth factors (such as TGF-β1, PDGF-AB and VEGF) and glycoproteins such as thrombospondin-1 during 7 days are found in PRF arranged as a dense fibrin scaffold. Leukocytes thus have a significant impact on the release of growth factors, immunological control, anti-infectious functions, and matrix remodelling during healing. All the clinical and radiographical parameters have shown that both the treatment modalities are equally effective in the periodontal regeneration of intrabony defects except for the Wound Healing Index (WHI) which was statistically significant at 7 days in the test group treated with amoxicillin incorporated PRF that gives the PRF additional benefit.

CONCLUSION

The present study concluded that both the treatment modalities are equally effective in treatment of intrabony defects, but the use of amoxicillin incorporated PRF significantly benefited in the initial wound healing necessary for successful surgical outcome. However, amoxicillin incorporated PRF did not lead to any post-operative complications or impaired tissue responses, indicating that antibiotics incorporated PRF can be used in the treatment of intrabony defects, avoiding the systemic administration of antibiotics post operatively. To assess the effectiveness of antibiotics incorporating PRF membrane in periodontal regeneration, additional controlled clinical trials with bigger sample sizes are needed.

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CONFLICT OF INETREST: None

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TABLE 1: PI and mSBI in Test and Control Groups at Baseline and 6 Months

	PI				mSBI			
	Control Site		Test Site		Control Site		Test Site	
	Mean	Std. Deviation	Mean	Std Deviation	Mean	Std. Deviation	Mean	Std Deviation
Baseline	1.787	0.223	1.775	0.38	1.562	0.436	1.783	0.373
6 months	0.75	0.213	0.587	0.29	0.598	0.302	0.696	0.193
P value	0		0		0		0	

TABLE 2: Clinical parameters in test and control site at baseline to 6 months

		Test Site		Control Site	
Parameters	Visit	Mean± SD	P Value	Mean± SD	P Value
PPD	Baseline	7.25±1.338	<0.000	7.125±1.356	<0.000
	6 months	4.375±1.187		4.625±1.302	
RAL	Baseline	11.125±1.885	<0.000	10±2.07	<0.000
	6 months	8.5±0.1.69		7.75±2.251	
RGML	Baseline	3.875±1.246	>0.170	2.875± 1.246	>0.170
	6 months	4.125±1.246		3.125±1.356	

Statistically significant at $p<0.05$

TABLE 3: Comparison of clinical parameters from baseline to 6 months between Control Group and Test Group

Parameters	**Test Site**	**Control Site**	**P value**
PPD	2.875±0.201	2.5±0.054	>0.224
RAL gain (mm)	.625±0.195	2.25±0.181	>0.079
RGML (mm)	0.25±0.00	0.25±0.11	>1.000

TABLE 4: Wound healing index of the treated sites at 7 and 14 days post-operatively

Wound healing index				
Duration		Test Site	Control Site	P value
7 days	Number of sites with a WHI score of 1	7	4	.045
	Percentage of sites with a WHI score 1	87.50%	50.00%	
14 days	Number of sites with a WHI score of 1	8	7	.149
	Percentage of sites with a WHI score 1	100%	87.50%	

TABLE 5. Radiographic parameters in test and control site at baseline to 6 months

		Test Site		**Control Site**	
Parameters	Visit	Mean± SD	P Value	Mean± SD	P Value
IBD depth	Baseline	4.75±0.90	<0.0001	4.13±0.75	<0.000
	6 months	2.45±0.87		2.2±0.67	
CEJ to BOD	Baseline	9.47±1.52	<0.0001	8.72±2.38	<0.000
	6 months	6.9±1.65		6.55±2.21	

TABLE 6: Comparison of radiographic parameters from baseline to 6 months between Control Group and Test Group

Parameters	**Test Site**	**Control Site**	**P value**
IBD depth reduction (mm)	2.3±0.027	1.937±0.086	>0.739
Bone defect fill (mm)	2.575±0.13	2.175±0.167	>0.581

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