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A Comparative Evaluation of Efficacy of 1.2% Atorvastatsin and 1.2% of Rosuvastatsin with Platelet Rich Fibrin in Intaosseous Alveolar Defects: A Randomized Clinical Trial

Dr. Anirban Chatterjee[1], Dr.Sneha Priya V[2], Dr. Koel Debnath[3], Dr.Vinayak Raghunathan[4], Dr. Praveen Jayaram[5]

[1]Professor and Head, Department of Periodontics, The Oxford Dental College, India

[2]Senior Resident, Safdarjung Hospital, New Delhi, India

[3]Senior lecturer, Department of Periodontics, The Oxford Dental College, India

[4]Senior lecturer, Department of Periodontics, The Oxford Dental College, India

[5]Reader, Department of Periodontics, The Oxford Dental College, India

Abstract: ***Aim: To determine the effectiveness of treating intra osseous defects with open flap debridement followed by placement of 1.2% Atorvastatin (ATV) gel and 1.2% Rosuvastatin (RSV) gel alone and mixed with autologous platelet rich fibrin (PRF). Materials and methods: 24 subjects with 82 periodontal intra osseous defects were selected and open flap debridement was carried out. Following 20 sites received 1.2% ATV gel (group I), 20 sites received 1.2% RSV gel (group II), 20 sites assigned to group III received 1.2% ATV gel mixed with PRF and group IV comprising of 20 sites received 1.2% RSV gel mixed with PRF. Site specific Plaque index, papillary bleeding index (PBI), probing depth reduction (PD) and clinical attachment level (CAL) gain and radiographic defect depth reduction was assessed at baseline 3, 6 and 9 months intervals. Statistical Analysis used: Kruskal Wallis test and Mann Whitney U test. Results: Comparing the results at 9 month interval all the groups has shown a significant reduction in PD reduction and CAL gain from baseline. The inter group analysis have shown no statistical significant difference in group I, II, III and IV in both clinical and radiographic parameters at a 9 months interval. Conclusion: The present study establishes a marked improvement in the clinical parameters and radiographic outcomes were noted with both 1.2% ATV gel and 1.2% RSV gel alone and Autologous PRF coated with 1.2% ATV gel and 1.2% RSV gel in the treatment of intra osseous defects.***

Keywords: Open flap debridement (OFD), Atorvastatin gel (ATV), Rosuvastatin gel (RSV) Autologous Platelet Rich Fibrin (PRF), intra osseous defects.

Key message: The present study demonstrates that, open flap debridement along with the use of either 1.2% ATV, 1.2% RSV gel orPRF coated with 1.2% ATV or 1.2% RSV, and presents with better clinical and radiographic outcomes.

1. Introduction

The etiology of periodontal disease is attributed to its multifactorial nature with the microbial colonization and host immune response playing the key role in the commencement and of the disease entity. Periodontal disease is manifested with loss of both hard as well as soft tissue structures which ultimately leads to loss of dentition. The ultimate goal of periodontal treatment is thus aimed at sustaining a functional masticatory apparatus.

Various treatment modalities have been tried and tested in the past and access flap surgery is acclaimed as a routine procedure after cause related therapy is accomplished. However, conventional access flap surgery alone falls short in dealing with regeneration of tissues which have been destroyed by the disease process.[1] A myriad variety of regenerative materials procedures have been employed in the past to achieve this ultimate goal, but most of these materials come with their inherent drawbacks such as its allogenecity, not being cost effective. [2] To combat these issues, recent literature suggests alternative aids such as the use of pharmacological compounds that can facilitate release of the necessary autogenous growth factors to enhance the bone growth, providing a cost effective approach to correct bone defects.

Statins are a class of cholesterol lowering drugs that restrain cholesterol biosynthesis by hindering the activityof 3-hydroxy-3-methyl-glutaryl-co-enzyme Areductase, which is a key enzyme in the mevalonate pathway. Although statin medication plays a principal role in lipid metabolism, it has also shown other pleiotropic effects which encompass its anti-inflammatory, antioxidant and osteoblastic differentiation potential. Among the various classes of statins, Atorvastatin has been found to be more effective compared to its counterparts as it decreases the tumor necrosis factor production and enhances the release of osteoblast differentiation markers which encompass makers such as alkaline phosphatase and osteocalcin. Rosuvastatin is also known as an important bone modulating agents along with anti-inflammatory and anti-oxidant agents. The osteo simulative nature of statins has proven its immense role in periodontal regeneration.

Pradeep et al (2013) investigated the effect of 1.2% ATV as an adjunct to scaling and root planingin the treatment of intra bony defects which exhibited a greater mean percentage of radiographic bone fill in the ATV group (35.49%) as compared to the placebo group (1.82%) after 9 months interval.[3]

RSV has already been found to enhance the clinical and radiographic condition of periodontium, in combination with PRF and porous-HA bone graft.[4] It has also shown to provide significant mean defect depth reduction (DDR) (48.58%) with greater clinical benefits when delivered locally into IBD sites.[5] In 2016 Pradeep et al has observed that PRF placement significantly enhanced the improvements in periodontal parameters than OFD alone. Addition of 1.2% RSV gel to PRF resulted in significantly greater CA level gain and PD and IBD depth reductions over 9 months compared to the other groups.[6]

Platelet-rich fibrin (PRF) described by Choukroun et al (2001), is a second-generation platelet concentrate which enables to secure fibrin membrane which has a high concentration of platelets and facilitate release of various growth factors.[4] Chang et al reported the effect of PRF on periodontal ligament fibroblasts and found that its incorporation caused and increase the activity of alkaline phosphatase with higher levels of osteoprotegrin. Along with the above mentioned activities placement of PRF in intra bony defects exhibited substantial pocket depth reduction and gain in the clinical attachment and bone fill at a recall of six months.[5] Martande-et-al which reported a significant probing depth reduction and relative attachment level gain along with radiographic defect depth reduction with PRF and 1.2% ATV group.[7]

To date very few studies have been reported addressing the combined regenerative potential of statin (ATV and RSV) alone and mixed with PRF approach.

Hence the present study was conducted to comparatively evaluate the clinical and radiographic parameters of treating intra-osseous defects using 1.2% Atorvastatin (ATV) gel, 1.2% Rosuvastatin (RSV) alone or mixed with 1.2% ATV gel and 1.2% RSV gel mixed with platelet rich fibrin.

2. Materials and methods

The above mentioned randomized clinical trial was conducted in the Department of Periodontics, The Oxford Dental College and Hospital, Bangalore. 31 subjects diagnosed with chronic periodontitis and with 97 sites with radiographic evidence of intra osseous defects meeting theinclusion criteria were chosen to participate in the study as shown in figure 1. Randomization software was used to randomly allocate the subjects based on the inclusion and exclusion criteria. Subjects aged between 20-55 years with minimum of 20 permanent teeth, periodontal pocket depth exceeding 5mm, clinical attachment loss of more than 3mm with radiographic evidence of intra osseous defect were included in the present study. Exclusion criteria comprised of systemically compromised subjects, those on medications (corticosteroids/ bisphosphonate therapy) that may interfere with wound healing, grade II and III mobile teeth, smokers, pregnant and lactating mothers and subjects who underwent any periodontal treatment within a period of 1 year.

Subjects fulfilling the above mentioned inclusion criteria were enrolled in the study and prior to the surgical protocol phase I therapy was performed. On the day of the procedure, the clinical and radiographic parameters were recorded with Radio visio graph (RVG) by paralleling technique and subjects were assigned to groups I, II or III and IV randomly by the principal investigator. Customized acrylic stents were used to record the pocket probing depths using a UNC-15 probe. Group I subjects were treated with open flap debridement alone followed by placement of 1.2% of ATV gel, group while group II subjects with OFD followed by placement of 1.2% RSV gel and group III subjectswere treated with OFD followed by placement of PRF coated with 1.2% ATV gel and group IV received PRF mixed with 1.2% of RSV gel following OFD.

2.1 Surgical procedure

Respective block anaesthesia/ infiltration were administered according to the area onto which the surgery was to be performed. Intra-sulcular incision followed by full thickness buccal and palatal / lingual flaps was elevated. Infected Granulation tissue was removed and any remaining plaque and calculus was gently removed with ultrasonic scalers. The intra osseous defects were assessed for their depths, by returning the customized acrylic stent along with a manual UNC-15 probe.
Following thorough open flap debridement flaps pre suturing with 3-0 silk suture were done. In group I and II 10 µl of 1.2% ATV and 10 µl of 1.2% of RSV respectively were placed into the defects with the help of blunt cannula. In group III and IV PRF coated with 1.2% of ATV and 1.2% of RSV were placed into the pre sutured defects. The flaps were approximated and sutured and periodontal dressing was used to cover the treated sites as observed in figure 2 and 3.

Post operative instructions were given verbally and the subjects were prescribed antibiotic (cap Amoxicillin 500 mg, TID, for five days) and analgesic (tab Diclofenac sodium 50 mg TID, for three days). Suture removal was done after 7 days and the subjects were instructed to restart their oral hygiene procedures.

2.2 Statistical analysis

The power of the study was 95 % with 31 subjects distributed in three treatment groups. Data were recorded as mean ± standard deviation for clinical and radiographic parameters. Statistical analysis was accomplished utilizing the Kruskal Wallis test and Mann Whitney U test and the following results were obtained.

3. Results

The randomized controlled clinical trial was conducted on 31 subjects, which included treatment for 97 intrabony defects which were randomly assigned i.e 25 intrabony defects to group I treated with 1.2% ATV gel, 24 intra bony defects in group II received 1.2% RSV gel, PRF coated with

1.2% of ATV gel were placed in 22 intra bony defects in group III and 25 intrabony defects were treated with (PRF coated with 1.2% of RSV gel) in group IV. Out of the 31 subjects included in this study, only 24 subjects completed the 9 month follow up interval with 6 subjects in each group with 82 sites. The statistical evaluation was performed on 82 sites.

The clinical parameters assessed included plaque index[8], papillary bleeding index,[9] probing pocket depth reduction, clinical attachment levels gain at baseline(0) followed by 3, 6, and 9 months. Radiographic defect depth reduction percentage was assessed using RVG which was taken at baseline (0) and compared it with 9 months follow up, with the help of the following formula

$$\text{Defect depth reduction percentage} = \frac{\text{Base line DD} - \text{9 months DD}}{\text{Base line DD}} \times 100$$

(DD = linear radiographic defect depth).[10]

Plaque Index and papillary bleeding index values revealed statistically significant decrease in all the four groups at 9 months post-surgery from baseline but with intergroup analysis no statistically significant differences between the four groups was noted. (Table 1 and 2)

Evaluation of clinical parameters of all the groups with respect to PPD has shown a significant reduction in PPD from baseline at 9 month interval p value <0.046 and in respect to CAL no significant differences in values were observed comparing group I, group II, group III and group IV (P<0.549) after 9 months intervals. (Table 3, 4 and figure 4 and 5)

With regard to the defect depth reduction, all the groups showed statistically significant improvement in defect depth reduction percentage with Group I (68%) and Group II (66.4%)and group III (72%) and Group IV (71.2%)but no statistical significant differences were observed when intergroup comparisons were evaluated. (Table 5 and figure 6)

4. Discussion

The definitive characteristic features of periodontal disease are associated with marked inflammation of gingiva, microbial infection causing alveolar bone deterioration, and subsequently leading to tooth loss, and thus suppression of the bone resorption rate is the goal for periodontal treatment. Open-flap debridement (OFD) or access flap surgery was among the earliest procedures recorded in the literature used and has shown to result in successful treatment of intrabony defects. According to a systematic review, by Graziani et al 2012, the average clinical attachment level (CAL) gain obtained with OFD alone was 1.65 mm, average probing depth (PD) reduction was 2.80 mm, gingival recession (REC) increase was 1.26 mm.[1]

PRF as described by Choukroun et al is a second generation platelet concentrate. It is believed to be superior to its previous counterparts attributed to the uncomplicated processing technique and better handing properties. PRF has been widely used both in medical and dental fields as it can facilitate wound healing, provides graft stabilization and improved haemostasis. In addition to that better organized fibrin network, the release of growth factors from the platelet concentrates has led to optimize clinical application.[11]

In the recent years there has been an increase in the evidence supporting a positive effect of statins on bone tissue. Studies relating the positive pleiotropic effects of statins in the oral tissues has comes from in vitro and animal studies (Junqueira et al. 2002, Stein et al. 2005, Wu et al. 2008)[12-14] followed by human trials (Pasco et al 2002, Mundy et al 1999, Lindy et al 2008, Cunha-Cruz J, Pradeep et al 2013, 2014).[3, 15-19] These studies have time and again emphasised the positive pleiotropic effect of statins. Contrary to the findings of the above studies, Saxlin, et al (2009)[20] observed the negative effects and stated that in patients with no plaque or gingival bleeding statin medication increases the likelihood of deepened periodontal pockets which could be attributed to disruption of immune homeostasis in periodontal tissues as a result of statin therapy predisposing periodontal tissue breakdown.

In the present study the evaluation of plaque index, and papillary bleeding index demonstrated a statistical significance reduction in the parameters from baseline to 6 months in all the groups. The positive results can also be ascribed to the subject motivation and education, provided prior to the surgical procedure and regular recall appointment where oral hygiene instructions were reinforced and mechanical debridement was carried out. Absence of bleeding on probing is the best predictor of periodontal health and caused due to decreased amounts of pro inflammatory cytokines. Authors like Kleemann and colleagues have shown that atorvastatin at doses higher than those required for cholesterol lowering, decrease basal and IL-1β-induced plasma human C-Reactive Protein (huCRP) levels.[21] This impact of statins to lower the pro-inflammatory state explains its potential implications in the management of inflammatory conditions like periodontitis.

The mean probing depth reduction seen in the present study showed statistical significance in all the three groups from baseline to 6 months. Group II (1.2% ATV gel alone) and group III (autologous platelet rich fibrin coated with 1.2% ATV) showed a statistical significance at 6 to 9 months interval, whereas group I (OFD alone) did not show any statistical improvement from 6 to 9 months interval. With respect to group I (OFD alone) the mean improvement of probing depth from baseline (0) to 9 months was 2.45mm, which is in agreement with the study by Graziani et al 2012[1] which showed an average probing depth reduction of 2.80 mm in relation to sites which were treated with debridement alone. Group II and group III in the present study showed, a mean probing depth reduction of 3.75mm and 3.90mm which is in agreement with the study conducted by Kinra et al. (2010) [22] which showed that when allograft was combined with simvastatin solution it resulted in significantly greater probing depth reduction, compared to the group where periodontal defects were treated with only placement to allograft. Deepening of the periodontal pocket occurs due to increase in the level of local inflammatory cells and MMP's which induces connective tissue destruction leading to periodontal disease (Oyarzun et al

2010).[23] Recently, ATV has also been reported to inhibit inflammatory cells and decrease the level of matrix metalloproteinases (MMPs).[24] Thus these factors may have contributed to improved probing pocket depth reduction with the addition of statin medication.

In the present study, CAL gain showed statistical significance in both group II (1.2% ATV gel alone) and group III (autologous platelet rich fibrin coated with 1.2% Atorvastatin gel) from baseline (0) to 9 months but results of the intergroup analysis demonstrated no statistical significance among the three groups at 9 months. This finding can be attributed to the case selection while randomizing the cases, that is because of the presence of recession at the baseline (0) the intergroup analysis of clinical attachment level did not reach statistical significance. Thus the present study is not in accordance to the study done by Martande et al 2016 which compared the effectiveness of 1.2% ATV gel with PRF showed an improvement in the relative attachment level compared to open flap debridement alone[7] and Pradeep et al in 2016 [6] and in 2015[25] has shown an improved with the use of RSV 1.2% mixed with autologous PRF.

Radiographic defect depth reduction percentage as with reduction in probing depth showed an improvement in all the three groups from baseline (0) examination; but group II (67%) and group III (72.3%) showed better results as compared to group I (46%).

Although, till date no effective consensus has been reached regarding the effect of ATV on bone metabolism (Braatvedt et al. 2004, Bone et al. 2007) [26,27] in the present study, ATV and RSV administration increased alveolar bone height. Intergroup analysis in the present study shows that in group III and IV (PRF coated with 1.2% ATV and PRF with 1.2% of RSV) radiographic defect depth reduction percentage was better (72% and 71.2%) than group I and II (68% and 66.4% respectively), and this can be explained on the grounds of autologous platelet rich fibrin which forms a network and facilitates the enhance delivery of growth factors in addition to the properties of statins.

Thus, within the constraints of the present study it can be demonstrated that, compared to the use of either 1.2% ATV gel alone (group I) and 1.2% of RSV gel alone (group II), autologous PRF coated with 1.2% ATV gel (group III) and autologous PRF coated with 1.2% RSV gel (group IV) presented with better clinical and radiographic outcomes, in the treatment of intra osseous defects.

The authors of the present study conclude that to overcome the short comings, more number of multicentre randomized clinical trial, with a larger sample size have to be carried out to optimize the dosage and authenticate the effectiveness of statin medication on periodontium.

5. Acknowledgments

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6. Conflicts of interest

No conflict of interest exists

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Table 1: Comparative evaluation of Plaque index values

	GROUP I		GROUP II		GROUP III		GROUP IV	
	p value	Sig	p value	Sig	p value	Sig	p value	Sig
Baseline(0)-3 months	0.010	S	0	S	0	S	0	S
3months-6 months	0.070	NS	0.007	S	0.005	S	0.003	S
6months-9 months	0.334	NS	0.058	NS	0.048	NS	0.037	NS

S- Significant; NS- Non Significant

Table 2: Comparative evaluation of papillary bleeding index

	GROUP I		GROUP II		GROUP III		GROUP IV	
	p value	Sig	p value	Sig	p value	Sig	p value	Sig
Baseline(0)-3 months	0.000	S	0.001	S	0.000	S	0.000	S
3months-6 months	0.000	S	0.006	S	0.002	S	0.002	S
6months-9 months	1.000	NS	0.011	S	0.180	NS	0.180	NS

S- Significant; NS- Non Significant

Table 3: Comparative evaluation of probing depths at 9 months interval

Patient	N	Min	Max	Mean	Std. Deviation	p value	Sig	Mann Whitney U test (with Group I)	Sig
Group I	21	2	4	3.3	0.657	0.046	S	0.017	S
Group II	20	2	4	2.8	0.696			0.027	S
Group III	20	2	4	2.85	0.671			0.04	S
Group IV	21	2	4	2.84	0.669			0.04	S

S- Significant; NS- Non Significant

Table 4: Comparative evaluation of clinical attachment level at 9 months interval

Patients	N	Min	Max	Mean	Std. Deviation	p value	Sig
Group I	21	1	5	2.32	0.995	0.549	NS
Group II	20	1	5	2.3	1.174		
Group III	20	1	5	2.4	1.353		
Group IV	21	1	5	2.42	1.333		

S- Significant; NS- Non Significant

Table 5: Comparative evaluation of defect depth reduction in Percentage

Groups	percentage of defect depth reduction	Mean	pvalue	Sig
Group I	68%	1.82	0.432	NS
Group II	66%	1.74		
Group III	72%	2.23		
Group IV	71.20%	2.08		

NS- Non Significant

Figure legends

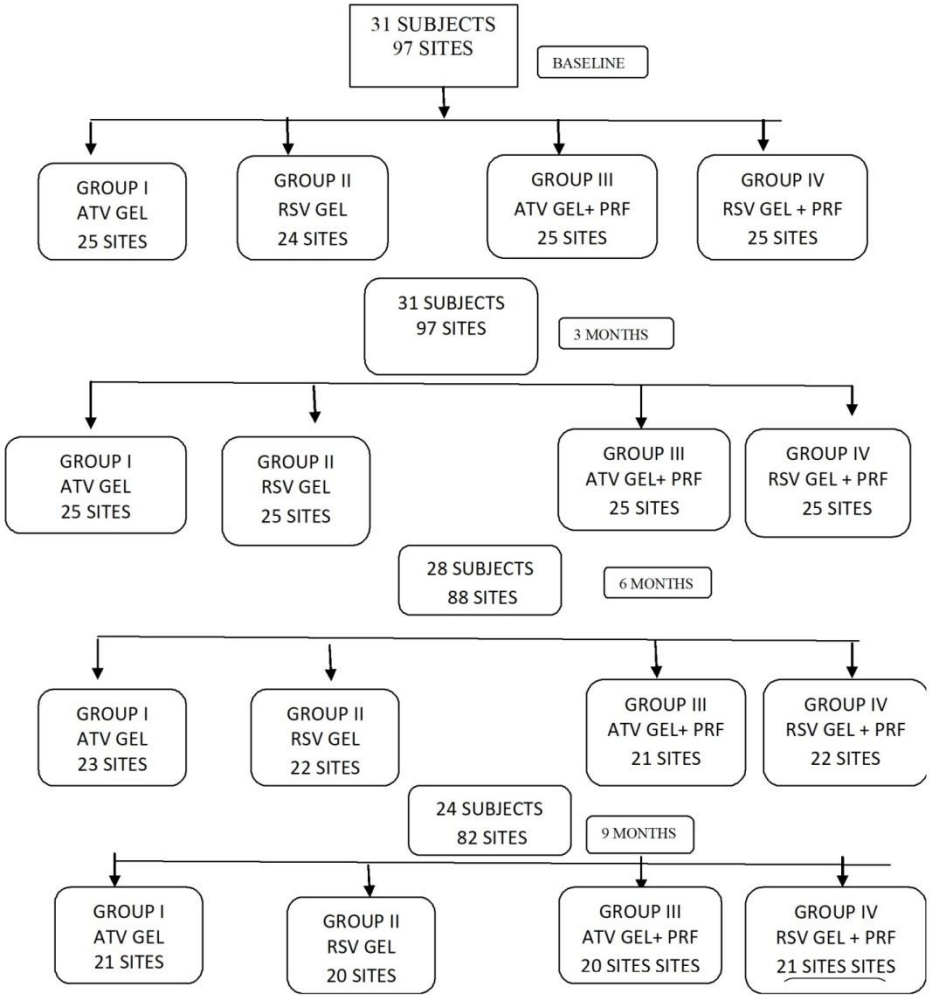


Figure 1: Flowchart

Figure 1: Flowchart

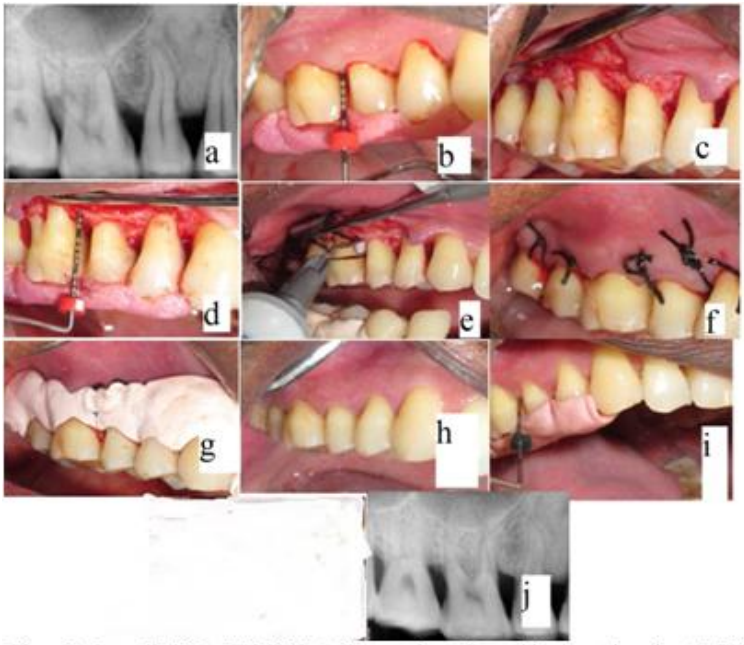
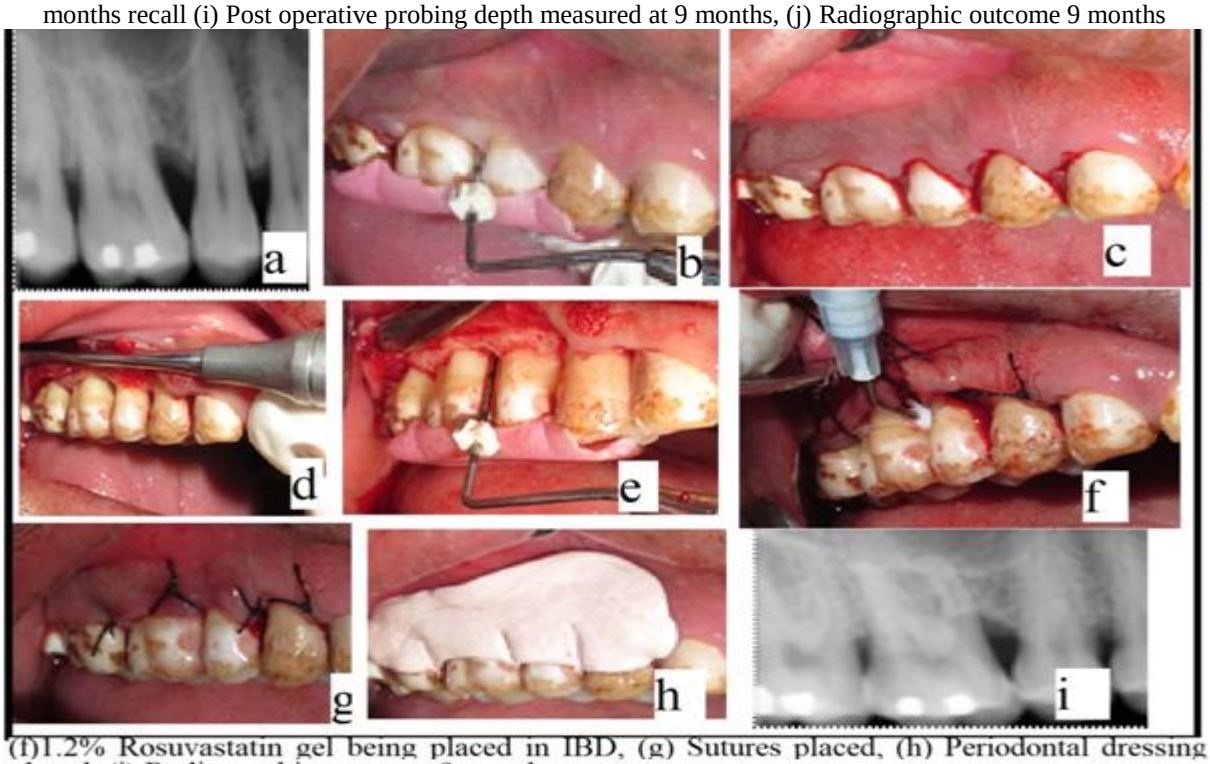


Figure 2: Group II (1.2% ATV+PRF): (a)Preoperative radiographic view at baseline, (b) Defect depth measured, (c) flap reflected; (d) defect depth measured (e)1.2% Atorvastatin gel being placed in IBD, (f) Sutures placed, (g) Periodontal dressing placed, (h) 9 months recall, (i) Radiographic outcome 9 months

Figure 2:

Group II (1.2% ATV+PRF): (a)Preoperative radiographic view at baseline, (b) Defect depth measured, (c) flap reflected; (d) defect depth measured (e)1.2% Atorvastatin gel being placed in IBD, (f) Sutures placed, (g) Periodontal dressing placed, (h) 9 months recall (i) Post operative probing depth measured at 9 months, (j) Radiographic outcome 9 months



(f)1.2% Rosuvastatin gel being placed in IBD, (g) Sutures placed, (h) Periodontal dressing placed, (i) Radiographic outcome 9 months

Figure 3: Group III (1.2% RTV+PRF): ((a)Preoperative radiographic view at baseline, (b) Defect depth measured, (c) incision placed, (d) flap reflected; (e) defect depth measured (f)1.2% Rosuvastatin gel being placed in IBD, (g) Sutures placed, (h) Periodontal dressing

Figure 3:

Group III (1.2% RSV+PRF): ((a)Preoperative radiographic view at baseline, (b) Defect depth measured, (c) incision placed, (d) flap reflected; (e) defect depth measured (f)1.2% Rosuvastatin gel being placed in IBD, (g) Sutures placed, (h) Periodontal dressing placed, (i) Radiographic outcome 9 months

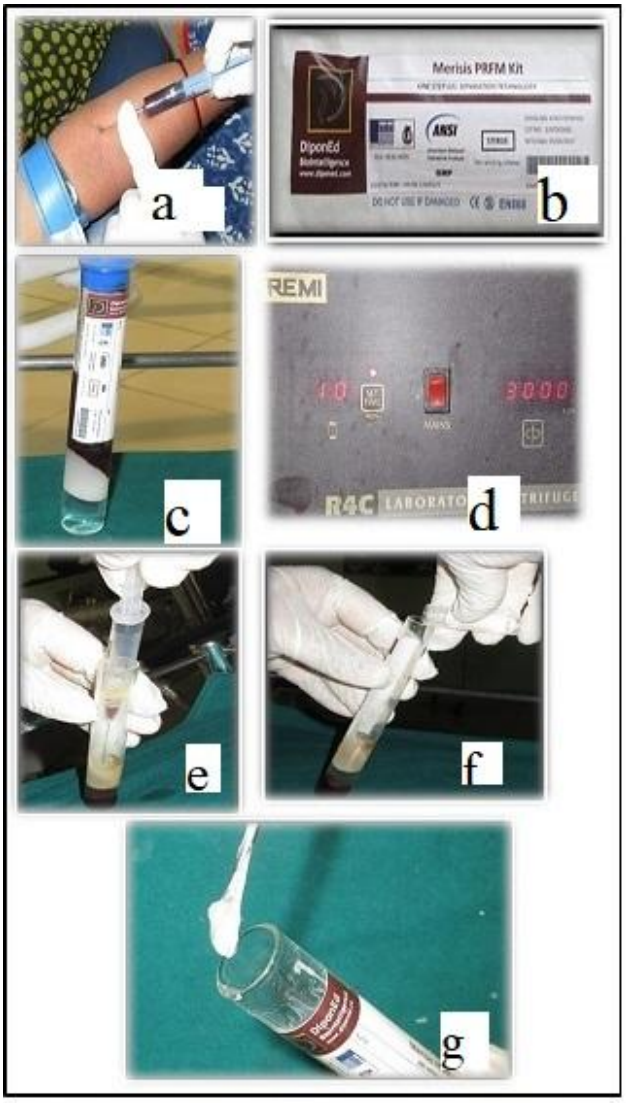


Figure 3: Platelet rich fibrin matrix (PRFM)

(a): blood withdrawn from antecubital vein; (b) Meresis tube used for preperation of PRFM; (c) withdrawn blood placed in the Meresis tube; (d) centrifugation done at 3000 rpm; (e) supernatant fluid withdrawn; (f) activator added; (g) PRFM gel obtained

Figure 4: Comparative evaluation of probing depths at 9 months interval

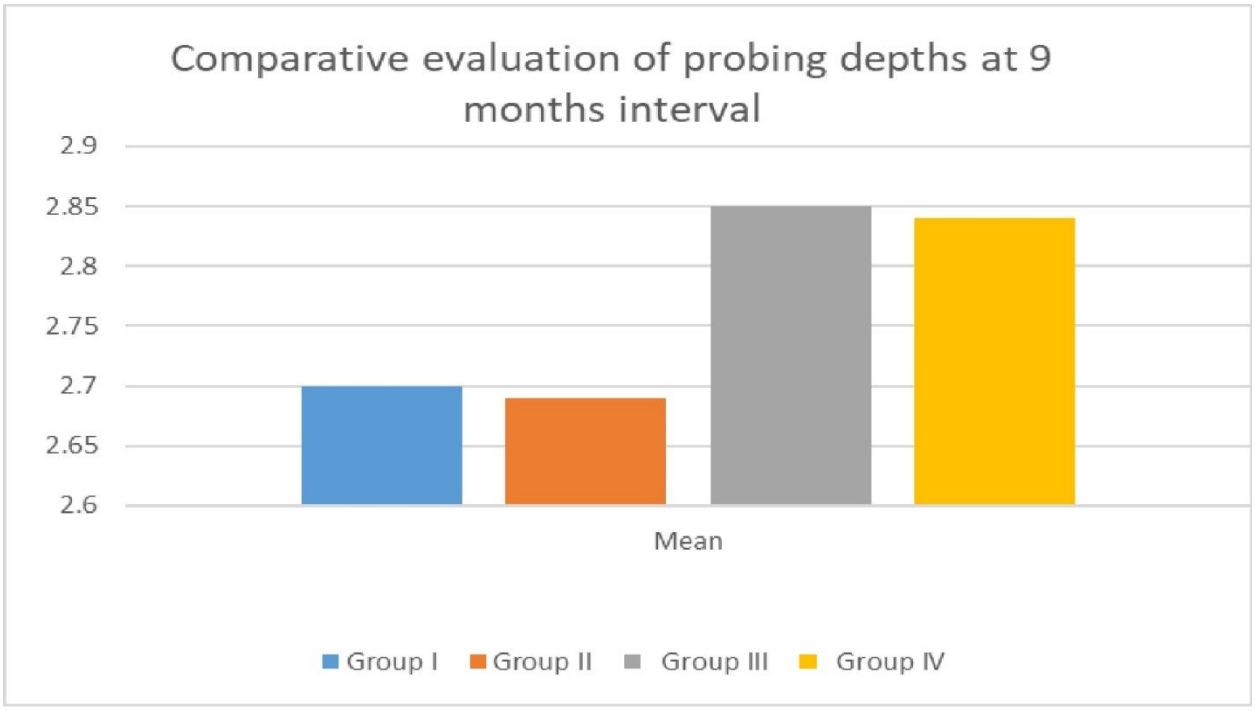


Figure 4: Comparative evaluation of probing depths at 9 months interval

Figure 5: Comparative evaluation of clinical attachment level at 9 months interval

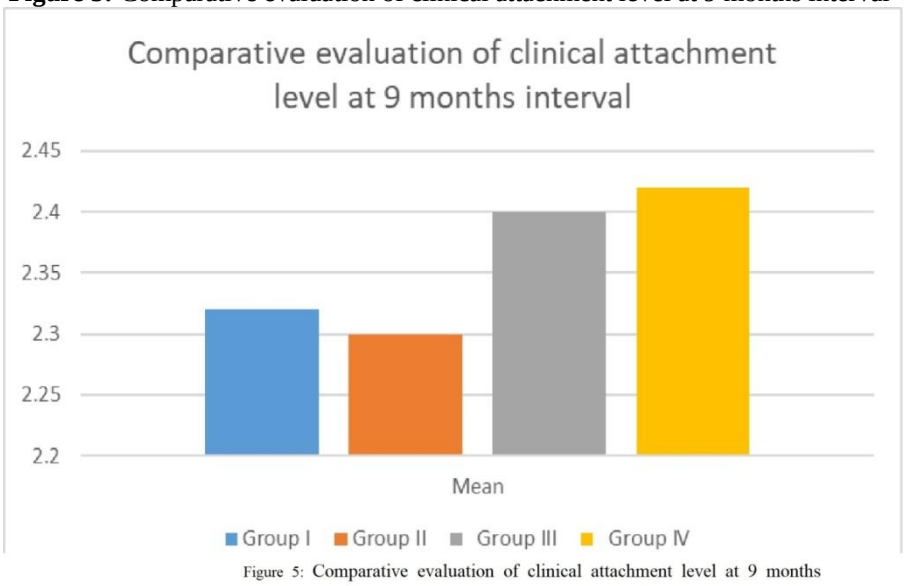


Figure 5: Comparative evaluation of clinical attachment level at 9 months

Figure 6: Comparative evaluation of defect depth reduction in Percentage

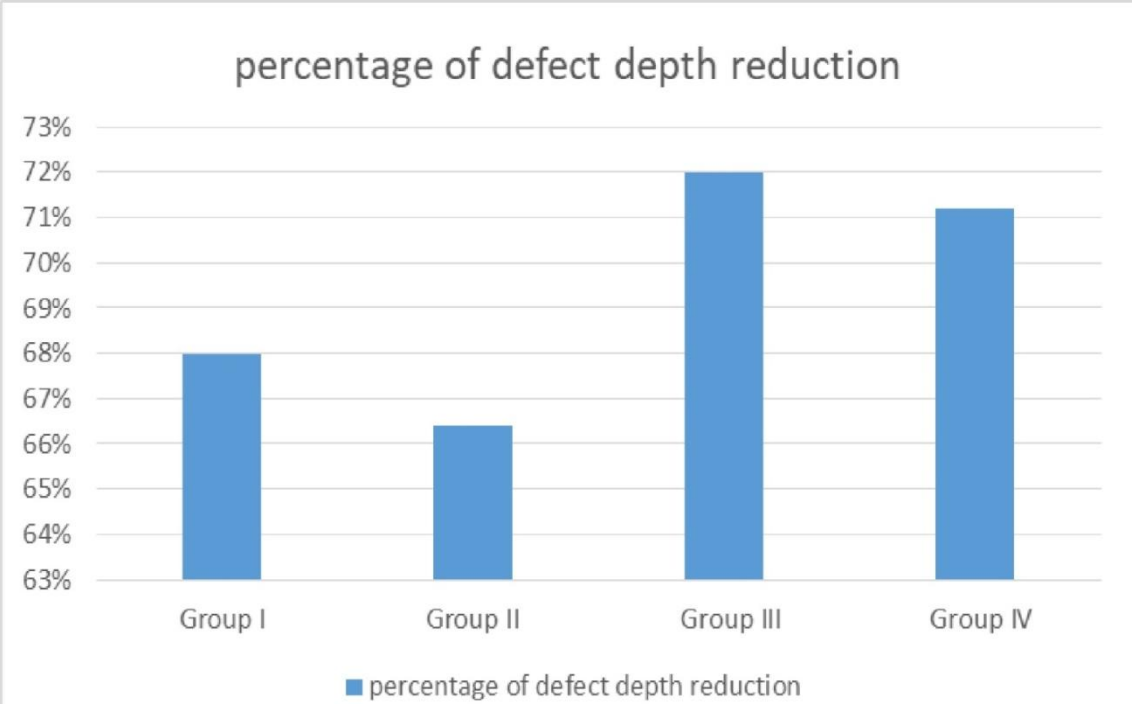


Figure 6: Comparative evaluation of defect depth reduction in PercentageComparative evaluation of