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Intrabony Defects Management Using Growth Factor Enhanced Matrix versus Platelet Rich Fibrin Utilizing Minimally Invasive Surgical Technique: A Randomized Control Study

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ABSTRACT

The present study aimed to assess the regenerative effect of minimally invasive surgical technique (MIST) alone or combined with growth factor enhanced matrix (GEM 21S) versus platelet rich fibrin (PRF) in the treatment of intra-bony defects clinically and radiographically.

Subject and Methods: 21 intra-bony defects in fifteen systemically healthy patients with moderate to severe chronic periodontitis were randomly classified into 3 groups, 7 sites each. Group I treated by MIST alone, group II treated by MIST +ethylenediamine-tetraaceticacid (EDTA) + PRF and group III treated by MIST+EDTA+GEM 21S. The clinical parameters including probing pocket depth (PPD), clinical attachment level (CAL) and bleeding on probing (BOP), were recorded at baseline, 3, 6 and 9 months' post-surgery. Cone beam computed tomography (CBCT) was performed at baseline and 9 months' post-surgery to evaluate bone level and bone density.

Results: Group II showed the marked improvements in clinical parameters followed by group III; while group I showed the least improvements. CBCT analysis showed statistically significant improvement in bone level, area of defect (AD) and bone density (BD) for the three studied groups at 9 months as compared to the mean baseline value with no significant differences between them at 9 months' period. However, group III showed the best improvement followed by group II and group I.

Conclusion: MIST with or without regenerative materials yielded improvement clinically and radiographically. The adjunctive use of PRF or GEM 21S provided superior benefits on the outcome of MIST for the treatment of intra-bony defects.

Key words: Chronic periodontitis, Intra-bony defects, minimally invasive surgical technique, Platelet rich fibrin, Growth factor enhanced matrix 21S, Cone beam computed tomography

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INTRODUCTION

Periodontal regenerative techniques include soft tissue grafts, bone grafts, root bio modifications, and guided tissue regeneration (GTR). The introduction of bio-mimetic agents, such as platelet rich plasma (PRP), platelet derived growth factors (PDGFs), bone morphogenic proteins (BMP), and other growth factors have given new promise for better outcomes in periodontal regeneration [1].

A convenient technique to obtain a high concentration of PDGFs is by preparing autologous platelet-rich protein (PRP) which is considered the first generation of platelet concentrate. A second generation of platelet concentrate is called platelet-rich fibrin (PRF) [2]. The PRF clot forms a strong natural fibrin matrix, which concentrates almost all the platelets and growth factors of the blood harvest [3]. This unique structure act as a vehicle for carrying cells, cell migration and proliferation, that are essential for tissue regeneration. Many growth factors, such as platelet derived growth factor (PDGF), transforming growth factor (TGF-β), vascular endothelial growth factor (VEGF), insulin growth factor (IGFs), and fibroblast growth factor (FGF) are released from PRF [1].

New and superior wound healing and bone regeneration technology termed growth factor enhanced matrix (GEM 21S) has recently become available for clinical use. This graft material consists of a concentrated solution of pure

recombinant human platelet derived growth factor (rh-PDGF-BB), the synthetic form of the body's key natural wound healing stimulator PDGF-BB and an Osteoconductive matrix which is beta-tricalcium phosphate (β-TCP) that is approved by Food and Drug Administration (FDA) for human application [4]. This graft material is a highly porous and resorb able matrix that provides a three-dimensional scaffold which acts as a framework for bone ingrowth, preventing the collapse of the soft tissues and promotes stabilization of the blood clot, thus facilitating bone healing [5].

The conventional periodontal surgery showed extensive tissue reflection which could result in attachment loss and lead to thermal sensitivity, food impaction and compromised esthetics [6,7]. Nowadays, a new periodontal surgical approach known as minimally invasive surgery (MIS) was proposed by Cortillini et al. [8]. They have the ability to perform a conventional surgical procedure utilizing a surgical opening that is smaller than the conventional access to achieve the same or better outcomes with less post-operative discomfort, more rapid healing, less morbidity, reduction in surgical chair time [9,10].

The background foundations for a novel surgical approach for periodontal regeneration (MIST) blended the concepts of MIS with the application of the papilla preservation techniques and the use of passive internal mattress sutures to seal the regenerating wound from the oral environment [11].

Accordingly, the present study was conducted to assess the effect of MIST combined with GEM 21S versus PRF in the treatment of the contained intra-bony defects clinically and radiographically.

MATERIALS AND METHODS

Trial plan

All patients were selected from the outpatient Periodontology Clinic, Faculty of Dentistry, Tanta University. They were diagnosed with moderate to severe chronic periodontitis according to Armitage criteria [12] and stage II/III grade B according to the new classification [13]. The age ranged between 30 and 55 years. We explained our work to them and took consenting from all of the participants under supervision of the Ethics committee of Faculty of Dentistry, Tanta University and Clinical trial.gov ID: NCT04786327.

Inclusion criteria

At least one tooth with PPD and CAL loss of ≥ 5 mm associated with an intra-bony defect of ≥ 2 mm according to Cortellini et al. [8].

Exclusion criteria

- Cases with poorly controlled Diabetes Mellitus and other conditions need antibiotic prophylaxis.
- Smokers.
- Pregnant patients.
- Patients with aggressive periodontitis.

Clinical examination and Radiographical outcome variables

Clinical parameters were measured at baseline, 3, 6 and 9 months following surgical treatment including: probing pocket depth (PPD) [14], clinical attachment level (CAL) [14] and bleeding on probing (BOP) [15]. Occlusal stent was fabricated to be used for standardization as a fixed reference point and fixed angulation for accurate positioning of the probes along the study evaluation periods Figure 1. CBCT was taken to measure the total depth of the intra-bony component of the defect (INFRA) [16], area of the defect (AD) and bone density using Hounsfield unit (HU).

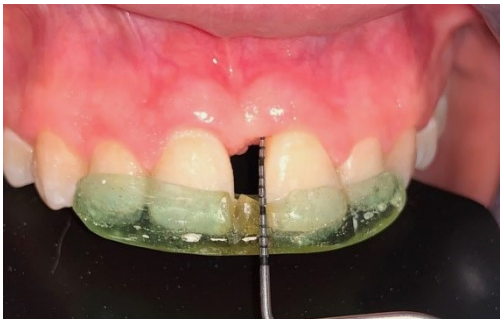

Figure 1: Fabricated occlusal stent for standardization as a fixed point and angulation for accurate positioning of the probe.

Sites grouping

Full mouth SRP was done followed by a comprehensive oral hygiene instruction. Occlusal therapy was performed as a part of periodontal therapy. Re-evaluation was conducted after one month to evaluate patient's response to phase I therapy and to find if surgery is needed.

A total of 21 interproximal intra-bony defects in fifteen patients with moderate to severe chronic periodontitis (Stage II/III Grade B) were randomly classified into three groups 7 sites each by using sealed envelopes method as follow:

- Group I: treated by using MIST (Control group).
- Group II: treated by using MIST with root conditioning (EDTA) and PRF (Test group).
- Group III: treated by using MIST with root conditioning (EDTA) and GEM 21S (Test group).

PRF preparation

10 ml of blood was drawn from the patient and collected in a sterile glass test tube without anti-coagulant. Immediately centrifuged using centrifuge machine at 3000 rpm for 10 minutes. The result was a fibrin clot located in the middle of a mass of a cellular plasma in the top and red cell layer in the bottom. The fibrin clot was carefully removed from the tube with tweezers then putted in sterile cup. PRF buffy coat layer was then grasped to be inserted in defects to treat group II (Figures 2 and Figure 3).

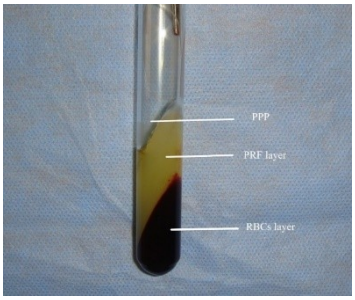

Figure 2: Different layers of Platelet rich fibrin (PRF).

Figure 3: Preparation of PRF from patient own blood.

Surgical procedure

We followed the surgical technique explained by Cortellini et al. [17] which included small flap elevation and interdental papilla incision, transverse in wide inter dental space or diagonal in short space [18] (Figure 4A and 4 4B).

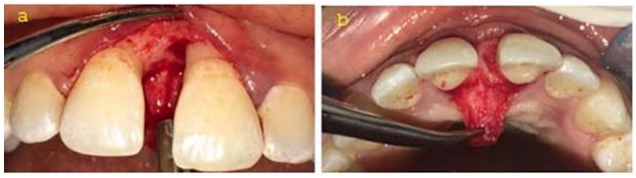

Figure 4A: Contained defect buccal view. 4B): Palatal view.

Full thickness flaps were therefore elevated with minimal mesiodistal and corono-apical. Vertical and periosteal incisions were avoided. Pocket epithelium and granulation tissue adherent to the inner surfaces of the flaps were carefully removed with micro-surgical scissors and mini-curettes to provide full access and visibility to the root surfaces (Figure 5A and 5B).

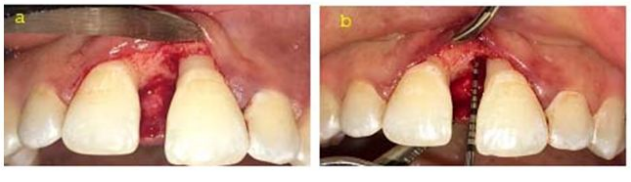

Figure 5A: Surgical site after degranulation and calculus removal. 5B) Intra-surgical measurement of intra-bony defect.

The defect was sutured in group I (MIST). While in group II (PRF) and group III (GEM 21S), the exposed root surfaces were conditioned by EDTA gel for two minutes to allow to remove the smear (Figure 6A and B).

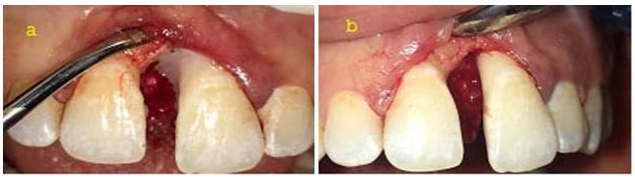

Figure 6A: Surgical site after application of EDTA. 6B: After washing of EDTA and drying of root.

After thoroughly rinsing the root surfaces with saline, PRF was directly applied to fill the defect in group II. While in group III, β-TCP granules were mixed with rh-PDGF-BB and allowed to sit for 10 minutes to permit binding of the rh-PDGF-BB protein to the β-TCP and ensure saturation before the graft was placed into the defect [19] (Figure 7A and B). Then, the buccal and lingual flaps were repositioned to their original level without any tension in the healing area and sutured using monofilament polypro line 6-0 with single modified internal mattress suture to reach primary closure of the papilla. The areas were then packed by periodontal dressing for 10 days (Figure 8).

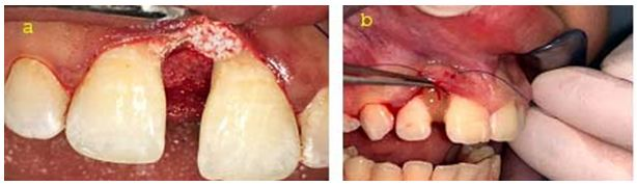

Figure 7A: Intra-bony defect filled with GEM21S (Group III). 7B: intra-bony defect filled with PRF (Group II).

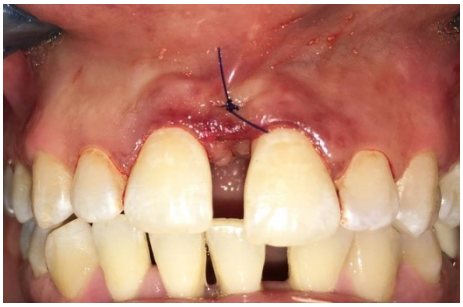

Figure 8: Flap closure with internal mattress suture.

Post-operative care

Augmentin 1gm once per day and Ibuprofen 400 mg twice daily were prescribed to the patients for one week. Subjects were ordered to wash by 0.12% Chlorhexidine (CHX) three times per day for one week. The subjects were ordered to avoid brushing, flossing or chewing on the treated area for periods of 3-4 weeks.

All subjects were recalled for professional prophylaxis, and oral hygiene instructions once a month until the final assessment 9 months' post-surgery. They also advised to seek for consultation if they had postoperative edema, hematoma, bleeding or any other complications.

Data analysis

The collected data was organized, tabulated and statistically analysed using computer software statistical package for social science (SPSS version 20).

The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level.

RESULTS

At baseline the three groups showed no significant differences regarding the clinical and radiographical parameters as evidenced by their mean baseline values (P>0.05).

Clinical results

The three studied groups showed statistically significant improvement in PPD, CAL and BOP at 3, 6- and 9-months post-surgery as compared to the mean baseline value (P ≤ 0.05) (Tables 1 to Table 3).

The intergroup comparison demonstrated non-significant differences between the studied groups for all clinical parameters at all study evaluation periods (P>0.05) however, a statistically significant improvement in the mean PPD reduction and CAL gain were observed at 9 months (P<0.05) between group I and group II in favour to group II.

Table 1: Effect of different treatment modalities on the mean probing pocket depth (PPD) in mm at the study evaluation periods.

Time of assessment	Group I MIST (n=7)	Group II MIST +EDTA+PRF (n=7)	Group III MIST +EDTA+GEM 21S (n=7)	ANOVA		Tukey's test		
				F	P	P1	P2	P3
Baseline Mean ± SD	5.29 ± 0.49	6.0 ± 1.41	5.43 ± 0.79	1.05	0.37	0.377	0.96	0.53
3 Months Mean ± SD	3.57 ± 0.53	3.43 ± 1.40	2.71 ± 1.60	0.921	0.416	0.976	0.43	0.55
PPD reduction at 3ms	1.71 ± 0.49	2.57 ± 1.51	2.71 ± 1.11	2.964	0.227	NS	NS	NS
6 Months Mean ± SD	3.0 ± 0.82	2.57 ± 0.79	2.43 ± 1.27	0.639	0.539	0.699	0.53	0.96
PPD reduction at 6ms	2.29 ± 0.49	3.43 ± 1.51	3.0 ± 0.82	4.047	0.132	NS	NS	NS
9 Months Mean ± SD	2.71 ± 0.76	2.29 ± 0.49	2.0 ± 1.0	1.5	0.25	0.567	0.23	0.77
PPD reduction at 9ms	2.57 ± 0.53	3.71 ± 1.25	3.43 ± 0.79	6.698*	0.035*	0.031*	0.06	1
Paired t-test	P0<0.05*	P0<0.05*	P0<0.05*					
MIST: Minimally invasive surgical technique								
EDTA: Ethylenediamine-tetraaceticacid								
GEM21S: Growth factor enhanced matrix 21S								
PRF: Platelet rich fibrin								
n=Number of patients								
Data expressed by Mean ± Standard deviation (X ± SD)								
Comparison of each period to baseline using paired t-test								
F: ANOVA test, pairwise comparison between each 2 group was done using Post Hoc-Test (Tuky)								
p: p value for comparing between the three studied groups								
p1: p value for comparing between Group I and Group II								
p2: p value for comparing between Group I and Group III								
p3: p value for comparing between Group II and Group III								
*: Statistically significant at P ≤ 0.05								
**: Highly significant at P ≤ 0.001								
Non-significant at P > 0.05								

Table 2: Effect of different treatment modalities on the mean clinical attachment level (CAL) in mm at the study evaluation periods.

Time of assessment	Group I MIST (n=7)	Group II MIST +EDTA+PRF (n=7)	Group III MIST +EDTA+GEM 21S (n=7)	Kruskal Wallis test		Dunn's for multiple comparisons test		
				H	P	P1	P2	P3
Baseline Mean ± SD	5.14 ± 1.21	4.86 ± 1.35	5.43 ± 0.79	0.265	0.876	NS	NS	NS
3 Months Mean ± SD	3.86 ± 1.35	2.29 ± 1.70	3.29 ± 1.25	3.697	0.157	NS	NS	NS
CAL gain at 3ms	1.29 ± 0.49	2.57 ± 1.51	2.14 ± 0.69	5.466	0.065	NS	NS	NS
6 Months Mean ± SD	3.14 ± 1.35	1.43 ± 1.62	3.0 ± 1.0	4.686	0.096	NS	NS	NS
CAL gain at 6ms	2.0 ± 0.58	3.43 ± 1.51	2.43 ± 0.53	5.886	0.053	NS	NS	NS
9 Months Mean ± SD	2.86 ± 1.21	1.14 ± 1.21	2.57 ± 0.79	6.295*	0.043*	0.019*	0.688	0.052
CAL gain at 9ms	2.29 ± 0.76	3.71 ± 1.25	2.86 ± 0.69	7.874*	0.020*	0.005*	0.116	0.22
Paired t-test	P0<0.05*	P0<0.05*	P0<0.05*					
MIST: Minimally invasive surgical technique								
EDTA: Ethylenediamine-tetraaceticacid								
GEM21S: Growth factor enhanced matrix 21S								
PRF: platelet rich fibrin								
n=number of patients								
Data expressed by Mean ± Standard deviation (X ± SD)								
Comparison of each period to baseline using paired t-test								
F: ANOVA test, pairwise comparison between each 2 group was done using Post Hoc-Test (Tuky)								
p: p value for comparing between the three studied groups								
p1: p value for comparing between Group I and Group II								
p2: p value for comparing between Group I and Group III								
p3: p value for comparing between Group II and Group III								
*: Statistically significant at P ≤ 0.05								
**: Highly significant at P ≤ 0.001								
Non-significant at P>0.05								

Table 3: Effect of different treatment modalities on the mean % bleeding on probing (BOP) score at the study evaluation periods.

Time of assessment	Group I MIST (n=7)	Group II MIST +EDTA+PRF (n=7)	Group III MIST +EDTA+GEM 21S (n=7)	Chi Square		Pairwise comparison		
				χ2	MCp	FEp1	FEp2	FEp3
Baseline	7 (100.0%)	7 (100.0%)	7 (100.0%)	-	-	-	-	-
3 Months	2 (28.6%)	0 (0.0%)	2 (28.6%)	2.486	0.487	0.462	1	0.462
6 Months	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	-	-	-	-
9 Months	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	-	-	-	-
Paired t-test	P0<0.05*	P0<0.05*	P0<0.05*					
MIST: Minimally invasive surgical technique								
EDTA: Ethylenediamine-tetraaceticacid								

Post Hoc Test (Dunn's for multiple comparisons test)
GEM21S: Growth factor enhanced matrix 21S
PRF: platelet rich fibrin
n=number of patients
Data expressed using No (%)
χ2 Chi square test MC: Mon Carlo FE: Fisher Extract
pairwise comparison between each 2 groups was done using Chi square test
p: p value for comparing between the three studied groups
p1: p value for comparing between Group I and Group II
p2: p value for comparing between Group I and Group III
p3: p value for comparing between Group II and Group III
*: Statistically significant at P ≤ 0.05; **: Highly significant at P ≤ 0.001; Non-significant at P > 0.05

Radiographic evaluation results

There was significant reduction in the mean value of defect depth (DD) for all three groups after surgery compared to baseline at 9 months (P < 0.05) (Table 4 and Figure 9).

There was a statistically non-significant difference between all the groups at 9 months' post-surgery (p>0.05). However, group III showed the highest DD reduction followed by group II while group I showed the least reduction.

Regarding the defect area (DA) results showed a statistically significant reduction in the mean values of DA at 9 months as compared to their baseline values for all groups (P ≤ 0.05) (Table 5 and Figure 10).

However, there was a statistically non-significant difference between all groups at 9 months' study interval (p>0.05) and group III showed the highest DA fill mm2 followed by group II while group I showed the least DA fill.

The radiographic results of bone density revealed that the mean values of BD have been improved for the three studied groups, this improvement was statistically significant when comparing baseline to 9 months' post-surgery (P ≤ 0.05) (Table 6 and Figure 11).

There was a statistically non-significant difference between three groups at 9 months post-operatively (P=0.056). However, group III showed the highest bone fill followed by group II while group I showed the least bone fill.

Table 4: Comparison between the three studied groups according to total depth of the intra-bony component of the defect (INFRA) in mm at baseline and 9 months' post-surgery.

Time of assessment	Group I MIST (n=7)	Group II MIST +EDTA+PRF (n=7)	Group III MIST +EDTA+GEM 21S (n=7)	Kruskal Wallis test		Dunn's for multiple comparisons test		
				H	p	p1	p2	p3
Baseline Mean ± SD	2.06 ± 1.80	1.81 ± 1.72	3.48 ± 1.27	4.727	0.094	0.295	0.324	0.457
9 Months Mean ± SD	1.17 ± 0.92	0.83 ± 0.55	2.38 ± 1.67	4.13	0.127	NS	NS	NS
p0	0.018*	0.028*	0.018*					
Defect depth reduction Mean ± SD.	0.89 ± 1.01	0.99 ± 1.24	1.10 ± 0.92	0.618	0.734	NS	NS	NS
MIST: Minimally invasive surgical technique								
EDTA: Ethylenediamine-tetraaceticacid								
GEM21S: Growth factor enhanced matrix 21S								
PRF: platelet rich fibrin								
n=number of patients								
H: H for Kruskal Wallis test, pairwise comparison between each 2 groups was done using								

Post Hoc Test (Dunn's for multiple comparisons test)

p: p value for comparing between the three studied groups

p1: p value for comparing between Group I and Group II

p2: p value for comparing between Group I and Group III

p3: p value for comparing between Group II and Group III

*: Statistically significant at P ≤ 0.05; **: Highly significant at P ≤ 0.001; Non-significant at P > 0.05

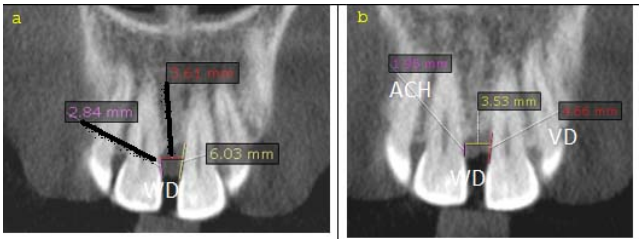

Figure 9A: Radiographic parameters at baseline (VD, ACH, WD). 9B: Radiographic parameters at 9 months (vertical depth (VD), alveolar crest height (ACH), width of the defect(WD).

Table 5: Comparison between the three studied groups according to defect area (DA) in mm2 at baseline and 9 months' post-surgery.

Time of assessment	Group I MIST (n=7)	Group II MIST +EDTA+PRF (n=7)	Group III MIST+EDTA +GEM 21S (n=7)	Kruskal Wallis		Dunn's for multiple comparisons test		
				H	P	P1	P2	P3
Baseline Mean ± SD	13.48 ± 3.54	13.27 ± 8.27	20.41 ± 6.61	5.128	0.077	NS	NS	NS
9 months Mean ± SD	10.55 ± 3.26	10.09 ± 4.77	16.24 ± 5.52	5.039	0.081	NS	NS	NS
p0	0.018*	0.018*	0.018*					
AD fill Mean ± SD	2.93 ± 2.46	3.17 ± 3.79	4.17 ± 1.63	2.293	0.318	NS	NS	NS

MIST: Minimally invasive surgical technique

EDTA: Ethylenediamine-tetraaceticacid

GEM21S: Growth factor enhanced matrix 21S

PRF: platelet rich fibrin

n= number of patients

H: H for Kruskal Wallis test, pairwise comparison between each 2 groups was done using

Post Hoc Test (Dunn's for multiple comparisons test)

p: p value for comparing between the three studied groups

p1: p value for comparing between Group I and Group II

p2: p value for comparing between Group I and Group III

p3: p value for comparing between Group II and Group III

*: Statistically significant at P ≤ 0.05; **: Highly significant at P ≤ 0.001; Non-significant at P > 0.05

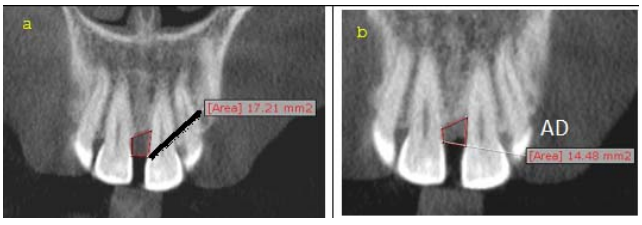

Figure 10A: Radiographic parameters at baseline defect area (DA). 10B: Radiographic parameters at 9 months' defect area (DA).

Table 6: Comparison between the three studied groups according to bone density (BD) in Hounsfield unit at baseline and 9 months' post-surgery.

Time of assessment	Group I MIST (n=7)	Group II MIST +EDTA+PRF (n=7)	Group III MIST +EDTA+GEM 21 (n=7)	Kruskal Wallis		Dunn's for multiple comparisons test		
				H	P	P1	P2	P3
Baseline Mean ± SD	350.9 ± 246.5	401.4 ± 260.5	756.5 ± 365.4	5.662	0.059	NS	NS	NS
9 months Mean ± SD	509.5 ± 265.9	645.6 ± 234.4	1027.0 ± 443.7	5.766	0.056	NS	NS	NS
p0	0.018*	0.018*	0.043*					
Bone fill Mean ± SD	158.61 ± 134.37	244.17 ± 128.65	270.43 ± 252.62	2.16	0.34	NS	NS	NS

MIST: Minimally invasive surgical technique

EDTA: Ethylenediamine-tetraaceticacid

GEM21S: Growth factor enhanced matrix 21S

PRF: platelet rich fibrin

n=number of patients

H: H for Kruskal Wallis test, pairwise comparison between each 2 groups was done using

Post Hoc Test (Dunn's for multiple comparisons test)

p: p value for comparing between the three studied groups

p1: p value for comparing between Group I and Group II

p2: p value for comparing between Group I and Group III

p3: p value for comparing between Group II and Group III

*: Statistically significant at P ≤ 0.05; **: Highly significant at P ≤ 0.001; Non-significant at P > 0.05

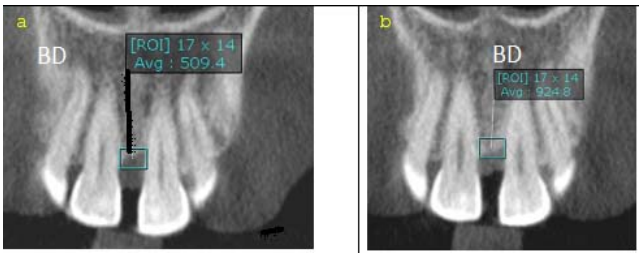

Figure 11A: Radiographic parameters at baseline bone density (BD). 11B: Radiographic parameters at 9 months' bone density (BD).

DISCUSSIONS

No adverse effects were observed in any patient during the follow up evaluation periods matching other clinical trials which have shown that neither GEM 21S nor PRF caused any allergic reactions throughout their study periods [19-21]. The results illustrated the improvement in all clinical parameters including PPD reduction, CAL gain, and decrease in BOP, with minimal recession in all groups which was maintained up to 9 months. It seems to be that MIST significantly enhanced the clinical outcomes of periodontal treatment in all groups. This was in accordance with systematic reviews conducted by Barbato et al. [22] Reedy et al. [23] meta-analysis performed by Liu et al. [24] and Perumal et al. [25]. Group II results showed the best improvement in PPD reduction and CAL gain followed by group III while group I showed the least improvement. The significant improvement in group I might be attributed to less surgical trauma, minimize flap elevation and reflection with minimal flap mobility which resulted in an extraordinary clinical healing capacity than the conventional flaps [17,22-28]. PPD and CAL reduction which was maintained till the end of the study evaluation periods regarding group II agrees with the slow sustained release of various growth factors and leukocytes cytokines present in the PRF matrix that have been proven to be released one month [29] which means that the PRF clot stimulates remodelling accelerating soft and hard tissue healing [30-33].

Concerning group III, PPD and CAL reduction was attributed to the presence of rh-PDGF-BB that possess neo-vessel formation and regenerative ability for gingival and PDL fibroblasts and cement oblasts initiating better connective tissue healing [34,35]. Additionally, it can be explained by the presence of β-TCP which considered being an effective delivery system as it entraps rh-PDGF-BB within its microspores, prolonging their action. In-vitro studies showed that β-TCP play a synergistic role in the mitogenic effects of PDGF on human PDL cells [36]. These results were in correspondence with several studies that showed significant improvements in PDD and CAL gain with soft tissue healing after application of rh-PDGF-BB (0.3 mg/ml) and β-TCP for treating bone deficiency [35]. On contrary, our results disagreed with a study performed by Liu et al. [24] to compare the clinical outcomes of MIST with EMD as a regenerative biomaterials and MIST alone in patients with intra-bony defects. The meta-analysis revealed no significant

difference regarding PPD reduction and CAL gain between the two studied groups. This could be attributed to different regenerative material (EMD) used in this meta-analysis.

The improvement in BOP may be attributed to the advantageous effect of MIST, the effect of the biomaterials used (PRF-GEM 21S), the suturing material and technique used and the patient compliance. Patient motivation and oral hygiene reinforcement might have a role to decrease the bacterial load which reduces the inflammatory response and disease activity, provides superior conditions for regeneration to occur [8].

A new observation regarding aesthetics was the minimal gingival recession in the three studied groups at all following up evaluation periods. This prove the advantageous effect of the novel approach (MIST) alone or with other regenerative biomaterials (PRF, GEM 21S).

Interestingly, the improvement in group II when compared to group III in all evaluated clinical parameters may be attributed to higher concentration of PDGF in PRF than GEM 21S. Additionally, the sustainability of PDGF in PRF is up to 10 days, [37] while in GEM 21S, the release of rh-PDGF-BB occurred more rapidly from β-TCP [38].

The three studied groups showed statistically significant improvement at the end of the study evaluation periods. In contrast, the intergroup results showed that, there was no significant difference when comparing all groups at baseline and after 9 months. However, group III showed the best improvement in bone level parameters followed by group II and group I which were nearly the same. Moreover, group III showed the highest bone density followed by group II while group I showed the least bone fill. The improvement in bone level and bone density in group I may be attributed to that the three-wall defects facilitates filling. These observed results were in context with, Liu et al. [24].

Regarding group II, the improvement may be because of PRF entraps circulating stem cells that differentiates into osteoblast phenotype30 and due to regenerative ability of PRF autogenous growth factors [21].

The highest favourable radiographic results regarding group III, may be explained by the physical effect of β-TCP as Osteoconductive three-dimensional framework which was improved by rh-PDGF that directed migration of osteoblasts coronal and into the defect leading to osteogenesis and defect fill [5,19].

CONCLUSION

Our research showed that MIST with regenerative materials is a useful surgical technique for regeneration of periodontal tissue which opened a new avenue in the field of periodontal therapy. The use of GEM 21 S with mist was proved to be effective, safe and biocompatible in the treatment of periodontal osseous defects clinically and radiographically.

LIMITATIONS AND FUTURE STUDIES

With the limitations in this study, in terms of small sample size, short term follows up evaluation periods with lack of experimental and histological evaluations, more precise results may be achieved if long-term assessment and expanded sample size were performed. Additionally, histological study on animals is needed to verify the bone and periodontal regeneration.

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