ORIGINAL RESEARCH

Effectiveness of Low-intensity Pulsed Ultrasound as an Adjunct to Periodontal Regenerative Therapy: A Randomized Controlled Clinical Trial

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Abstract

Aim: This study was performed to evaluate the effectiveness of low-intensity pulsed ultrasound (LIPUS) as an adjunct to periodontal regenerative therapy [open flap debridement (OFD) with or without bone graft (BG)] in intrabony defects of chronic periodontitis patients.

Materials and methods: A total of 40 angular periodontal defect sites were included in this study by recruiting 18 systemically healthy volunteers. Sample sites were randomly allotted to four groups: group I, OFD; group II, OFD + LIPUS; group III, OFD + BG; and group IV, OFD + BG + LIPUS. The clinical parameters such as plaque index (PI), gingival sulcus bleeding index (SBI), probing depth (PD), clinical attachment loss, radiographic depth of the defect site, and alkaline phosphatase (ALP) level in gingival crevicular fluid (GCF) were analyzed.

Results: When compared between the groups, there was no significant difference in clinical and radiographic parameters at 3 and 6 months of postevaluation, whereas ALP level showed a significant increase at 6 weeks in group II and group IV when compared to other groups.

Conclusion: It can be concluded that LIPUS did not improve periodontal regeneration in terms of clinical and radiographic parameters when used as an adjunct to periodontal regenerative therapy. But it has shown the potential to increase the ALP level in GCF.

Clinical significance: There is no added clinical benefit in the short-term usage of LIPUS in periodontal therapy.

Keywords: Alkaline phosphatase, Gingival crevicular fluid, Intrabony defect, Low-intensity pulsed ultrasound, Periodontal regeneration, Periodontitis.

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Introduction

Periodontitis is a common oral disease in adults, which is characterized by the progressive destruction of the supporting tissues of the tooth leading to tooth loss.[1] It is considered an inflammatory disease influenced by bacteria in the biofilm around the teeth leading to loss of supporting tissues, namely the periodontal ligament, cementum, and alveolar bone.[2] The primary goal of periodontal therapy includes arresting the progress, preventing the disease recurrence, and regenerating the lost periodontal tissue.[3] The treatment of periodontal disease can range from nonsurgical periodontal therapy like scaling and root planing (SRP) alone or SRP either with systemic or local antimicrobial or anti-inflammatory agents to surgical flap debridement and regenerative therapy.[4–7] However, the reconstruction of the lost periodontal tissue is difficult due to the slow regeneration potential of the tissue and the unique structural characteristics of the periodontium. Thus, it is critical to developing new strategies to accelerate periodontal regeneration.

Low-intensity pulsed ultrasound (LIPUS) is a commonly used technique approved by the United States Food and Drug Administration for enhancing bone healing in fractures and nonunions.[8,9] In LIPUS, mechanical energy is transmitted transcutaneously into biological tissues as high-frequency (1.5 MHz) acoustical pressure waves.[10] This enhances tissue regeneration by inducing osteoblast differentiation, promoting cytokine secretion, stimulating extracellular matrix production and the deposition of calcium, and improving microcirculation.[11–13] *In vitro* studies have revealed that stimulation by LIPUS can enhance the expression of bone formation-related alkaline phosphatase, genes osteocalcin, and bone sialoprotein.[14–16] In addition, LIPUS has been reported to promote protein synthesis and calcium uptake in various osteoblastic cell lines.[17] It also intensifies cyclooxygenase-2 gene expression and, subsequently, endogenous prostaglandin E2 synthesis in various osteoblastic cell lineages, thus playing an important role in bone remodeling.[18] LIPUS significantly stimulated bone healing in tibial fractures[19] and the healing of distal radial bone fractures.[20] Likewise, LIPUS also enhanced healing rates after nonunion fractures.[21] It has been reported that LIPUS stimulated the differentiation of cementoblasts and the regeneration of cementum.[22,23] Similarly, LIPUS combined with guided tissue regeneration has a promising beneficial effect in the treatment of periodontal defects.[24] As LIPUS had beneficial effects on hard-tissue healing in humans and periodontal regeneration

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in canines, we hypothesized that it might accelerate periodontal regeneration in humans. Since there is no research to evaluate the effect of LIPUS on periodontal regeneration in chronic periodontitis patients, the present research is aimed to evaluate the effectiveness of LIPUS as an adjunct to periodontal regenerative therapy with or without BG in intrabony defects of chronic periodontitis patients.

Materials and Methods

This interventional study was a single-center, parallel, randomized, and double-blinded clinical trial. The research protocol was approved by the Institutional Ethical Committee and Review Board (SRB/SDMDS16PER/02). The trial was registered in Clinical Trial Registry-India (CTRI/2018/05/013707). Formal written informed consent was obtained from all those who agreed to participate voluntarily in the study after a thorough explanation of the procedures and risks involved. The research protocol follows CONSORT guidelines as well as the Helsinki Declaration for human research, as revised in 2013. The subjects recruited for the study were outpatients attending the Department of Periodontics, Saveetha Dental College, Chennai, Tamil Nadu. A total of 40 angular defect sites were included in this study by recruiting 18 systemically healthy subjects (nine males and nine females). The duration of the study was 6 months. Patients were enrolled in June 2018. The study ended in January 2019.

Inclusion Criteria

Patients with chronic periodontitis, according to the American Academy of Periodontology Classification, 1999, were considered for the study.[25] Intraoral periapical radiographs (IOPA) were taken to confirm the presence of appropriate intrabony defects for the selection of sample sites. Patients of age 25–60 years with interproximal intrabony defects ≥4 mm deep distance between alveolar crest (AC) and base of the bony defect (BD) on IOPA along with an interproximal PD ≥5 mm following phase I therapy (SRP) were recruited. If multiple sites were present in the same patient, only one site per quadrant was included in this study.

Exclusion Criteria

Patients with any systemic disease known to affect the outcome measure of the periodontal therapy, compromised immune system, pregnancy and/or lactation, smoking or the use of other tobacco products, those taking drugs known to interfere with wound healing, allergy or sensitivity to any medication to be used in the study, and those with unsatisfactory oral hygiene (PI >2) during the reevaluation after phase I therapy were excluded from the study.[26] Added teeth with gingival recession, Miller grade II or greater mobility, and a history of surgical periodontal therapy in the last 6 months were also excluded.

Sample Size Calculation

Since there was no previous data on the use of LIPUS on the human periodontium, the clinical and radiological parameters were not considered for sample size calculation. A sample size of 20 (five in each group) was calculated using G-Power with the power 80, α error 0.05 based on the study done by Leung et al. [27] by considering serum ALP level.

Presurgical Therapy

Each volunteer recruited for the study was given careful instructions on proper oral hygiene measures. Full mouth subgingival SRP was performed under local anesthesia. A total of 4 weeks following phase I therapy, periodontal status was evaluated to confirm the suitability of the sites for this study.

Randomization

The selected sample sites were randomly allotted immediately before surgery to four groups, group I, OFD; group II, OFD + L; group III, OFD + BG; and group IV, OFD + BG + LIPUS. Sites were randomized by computer-generated numbers with the website randomization.com (http://www.randomization.com) and allotted to four groups. Allocation concealment was done by a sealed envelope to avoid bias.

Outcome Parameters

Clinical parameters recorded before the surgical procedures included PD, clinical attachment level (CAL), and using customized acrylic stents with grooves to ensure a reproducible placement of William's periodontal probe (Hu-Friedy, Chicago, Illinois, United States of America). Site-specific PI and gingival SBI[28] were also recorded. Bone defect morphology was assessed with digital IOPA taken by long cone paralleling angle technique and standardization of position was done by individually customized occlusal putty stents and film holders to obtain reproducible images. Digital intraoral periapical radiographic images were taken with Durr Dental-photostimulable phosphor imaging plate size 2 as image receptor operating at 70 kVp, 7 mA, and 0.2 second exposure time. Linear measurement of the bone defect was measured with a 1 mm × 1 mm dental X-ray measuring grid of size similar to IOPA. The measurement was the difference between the distances from the cementoenamel junction (CEJ) to the AC and the distance from the CEJ to the base of BD. The number of grids involved in the angular defect was counted to calculate the defect depth; hence the accuracy was to the nearest 1 mm (Fig. 1).

GCF Assessment

Alkaline phosphatase (ALP) level was measured in GCF at baseline (prior to periodontal flap surgery). Prior to GCF collection, a supragingival plaque from each tooth was removed with cotton pellets, isolation of the site was carried out with cotton rolls, and gentle air drying of individual teeth was done. A total of 1 µL of GCF samples was collected with calibrated capillary tubes (5 µL tubes, Hirschmann ringcaps, Sigma Aldrich, United States), which were placed at the entrance of the crevice and transferred with a

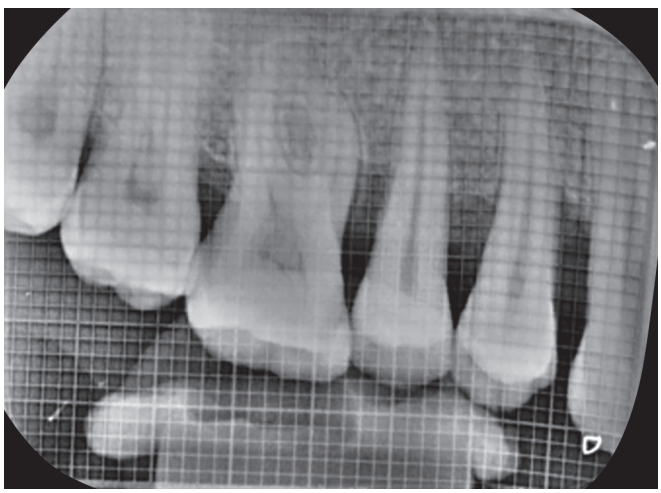

Fig. 1: Radiographic image with a grid placed

jet of air pressure into an Eppendorf tube containing 99 µL of PBS and stored at 20°C until further analysis. ALP levels in the samples were determined by using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (ELISA Kit, Elabscience, Texas, United States).

Surgical Procedure

After the administration of local anesthesia (lignocaine with adrenaline 1:2,00,000), buccal and lingual sulcular incisions were made, and mucoperiosteal flaps were reflected. The incision technique used to access the intrabony defect was an envelope intrasulcular without vertical incision. Incision was made using no. 15C blade. The incision extended one tooth mesial and one tooth distal to the sample site. Maximum interproximal soft tissue was preserved. Root planing followed by debridement of the defect was carried out using area-specific curettes (Gracey curettes, Hu-Friedy). No osseous recontouring was done. The concealed envelopes were opened immediately after the debridement of the defect site. Later, BGs (Advanced Biotech Osseograft–DMBM–Xenograft) were placed in sites belonging to groups III and IV. Repositioning of the mucoperiosteal flap was done, and the flap was secured using 4–0 nonabsorbable black-braided silk suture (Ethicon, Johnson, and Johnson, Somerville, New Jersey). Simple interrupted sutures were placed. Antibiotics and analgesics (amoxicillin 500 mg with lactobacillus 60 million spores, thrice per day; and diclofenac twice a day, for 3 days) and chlorhexidine digluconate mouthrinse (0.12%) twice daily for 3 weeks was prescribed.

One surgeon performed all the surgeries. An examiner other than the operator performed all the clinical measurements without knowledge of the treatment groups in order to ensure blinding.

LIPUS Application

The low-intensity pulsed ultrasound therapy was started for the groups' II and IV. The LIPUS was generated by an ultrasound therapeutic device designed and manufactured by Technomed Electronics, Chennai, India. The sample size was exposed to LIPUS (200 µs burst sine wave, frequency of 1.5 MHz, pulse repetition frequency of 1.0 kHz, intensity of 30 mW/cm^2)[22,29] by placing an ultrasound probe over the gingiva of intrabony defect site (Fig. 2). The LIPUS therapy was from postoperative day 1, the exposure was once a day for 20 minutes each time and every alternative day for 2 weeks.[30] The sites in group I and III were subjected to a sham treatment where the probe was inoperative to ensure blinding at the patient level.

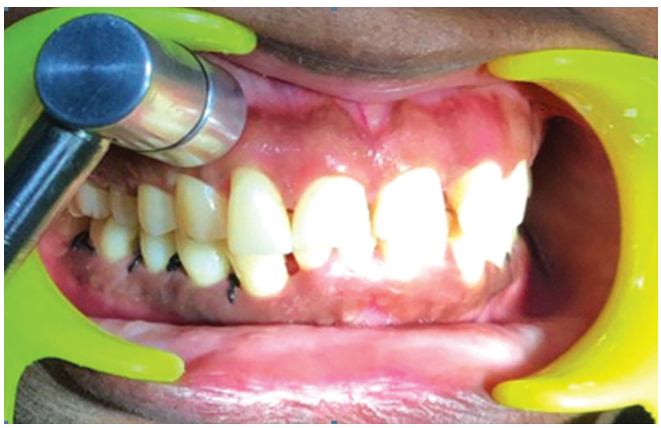

Fig. 2: Intraoral application of ultrasound probe

Postoperative Care

Sutures were removed 2 weeks postoperatively. Surgical wounds were gently cleansed with 0.12% chlorhexidine digluconate on a cotton swab. A gentle brushing with a soft toothbrush was recommended during the study period. All the patients were reexamined weekly for 1 month after surgery and then at 3 and 6 months. However, No subgingival instrumentation was attempted at any of these appointments. Postoperative care included reinforcement of oral whenever necessary.

Postsurgical Measurements

Alkaline phosphatase (ALP) level in GCF was examined 6 weeks after surgery. Postsurgical clinical and radiographic evaluation was performed 3 and 6 months after surgery. PD and CAL measurements were repeated with acrylic stents prepared earlier. SBI and PI were also recorded. For radiographic intrabony defect depth, IOPA of the same study site was carried out with putty stents and radiographic positioners.

Statistical Analysis

Clinical and radiographic parameters within the group were tested using Friedman's test for repeated measures. Groups were compared for treatment outcome at 3 months and 6 months using the Kruskal–Wallis test for variance. Change in ALP level was analyzed by Wilcoxon signed-rank test for paired data. Groups with significant differences were further tested with Mann–Whitney *U* test for *post hoc* analysis. The data were analyzed using software Statistical Package for the Social Sciences (SPSS) version 10.5, SPSS, Chicago, Illinois. The difference was statistically significant when $p \leq 0.05$.

Results

Out of 18 volunteers, four volunteers with six intrabony defect sample sites did not report after initial preparation. Hence, only 34 recruited sites completed the trial. All the sites were either three or two-walled defects (Table 1). During the course of the trial, all volunteers showed good compliance with uneventful healing postoperatively. Everybody showed a good soft tissue response to all treatment modalities. No adverse reactions, such as allergies or abscesses, were observed after the application of therapy, which confirmed the biocompatibility of the therapy. The periodontal status of the four groups was demonstrated using the mean and standard deviation for the appropriate clinical measurements PI, BI, PD, CAL, radiographic depth of defect site, and ALP level in GCF.

At baseline, all BI and PI scores were within clinically healthy parameters (score <1). The mean PI and BI were low and there were no statistically significant differences between the initial and 3 or 6 months or between the groups at all time periods (*p*-value >0.05) (Table 2). All four studied groups showed a statistically significant reduction in PD and CAL at 3 and 6 months when compared with the initial baseline value (*p*-value <0.05), but there was no statistically significant difference in mean PD between the groups at 3 and 6 months (*p*-value 0.85 and 0.65, respectively). Similarly, there was no statistically significant difference between the mean CAL of the four groups at any time period (*p*-value 0.94 and 0.81) (Table 3).

With regards to radiographic parameters, at 3 and 6 months, only group II (0.60 ± 0.89 and 0.40 ± 0.89) and group IV (1.97 ± 2.44 and 1.33 ± 1.37) showed a statistically significant reduction in

Table 1: Characteristics of the selected sample sites

	Group I		*Group II*		*Group III*		*Group IV*	
Sample	*Tooth number*	*Defect type*	*Tooth number*	*Defect type*	*Tooth number*	*Defect type*	*Tooth number*	*Defect type*
1	15	2-wall	16	3-wall	33	2-wall	43	3-Wall
2	24	3-wall	26	3-wall	15	3-wall	14	3-wall
3	21	2-wall	43	2-wall	14	3-wall	26	2-wall
4	26	2-wall	24	3-wall	37	2-wall	36	3-wall
5	26	3-wall	23	2-wall	35	3-wall	26	3-wall
6	26	3-wall	46	3-wall	46	3-wall	35	3-wall
7	26	2-wall	17	2-wall	16	2-wall	16	2-wall
8	26	2-wall	26	2-wall	35	2-wall	13	3-wall
9	Dropout		Dropout		36	2-wall	17	2-wall
10	Dropout		Dropout		Dropout		Dropout	

Table 2: Comparison of the BI and PI comparison among the four groups at different time intervals

	Group I	*Group II*	*Group III*	*Group IV*	*p-value*$^{++}$
			Gingival SBI		
Baseline	0.57 ± 6.16	0.60 ± 6.20	0.67 ± 4.14	0.76 ± 0.13	**0.1924**
3 months	0.89 ± 1.27	0.69 ± 2.32	1.01 ± 1.34	1.25 ± 1.38	0.6689
6 months	1.04 ± 2.27	0.61 ± 2.27	0.76 ± 4.79	0.97 ± 0.78	0.7839
p-value^{+}	0.5188	0.8187	0.2153	0.7470	
			PI		
Baseline	0.79 ± 9.18	0.78 ± 0.34	0.62 ± 9.33	0.76 ± 7.32	0.7229
3 months	0.64 ± 3.26	1.03 ± 0.29	0.68 ± 9.36	0.80 ± 0.40	0.2066
6 months	0.63 ± 8.32	0.68 ± 2.13	0.53 ± 9.24	0.67 ± 3.46	0.7565
p-value^{+}	0.3147	0.4029	0.4095	0.3114	

$^{+}$*p*-value for Kruskal–Wallis test comparing the values of different time periods within the group; $^{++}$*p*-value for the Friedman repeated analysis of variance (ANOVA) test comparing the values between the group at specific time

Table 3: Comparison of the PD and CAL between the groups at different time intervals

	Group I	*Group II*	*Group III*	*Group IV*	*p-value*$^{++}$
			PD in mm		
Baseline	8.13 ± 1.73	6.80 ± 1.92	6.86 ± 1.77	7.83 ± 3.98	**0.3116**
3 months	4.63 ± 1.77	4.00 ± 1.00	3.71 ± 4.49	4.33 ± 1.86	0.8538
6 months	4.00 ± 2.33	4.40 ± 1.14	3.57 ± 1.53	4.00 ± 2.10	0.6516
p-value^{+}	0.0035*	0.0351*	0.0204*	0.0372*	
			CAL in mm		
Baseline	8.25 ± 1.28	7.00 ± 2.35	6.80 ± 2.36	8.33 ± 1.33	0.3151
3 months	5.00 ± 1.60	4.40 ± 0.55	4.57 ± 1.53	5.00 ± 1.55	0.9445
6 months	4.38 ± 2.13	4.60 ± 1.14	4.16 ± 1.75	4.83 ± 1.72	0.8120
p-value^{+}	0.0042*	0.0142*	0.0130*	0.0422*	

$^{+}$*p*-value for Kruskal–Wallis test comparing the values of different time periods within the group; $^{++}$*p*-value for the Friedman repeated ANOVA test comparing the values between the group at specific time; *significant *p*-value ($p \leq 0.05$)

Table 4: Comparison of the radiographic measurement of depth of the defect site between the groups at different time intervals

	Group I	*Group II*	*Group III*	*Group IV*	*p-value*$^{++}$
Baseline	2.88 ± 1.36	2.00 ± 0.71	3.71 ± 2.21	3.17 ± 2.93	0.1253
3 months	1.25 ± 1.16	0.60 ± 0.89	2.71 ± 2.54	1.97 ± 2.44	0.1039
6 months	0.88 ± 1.13	0.40 ± 0.89	2.57 ± 2.44	1.33 ± 1.37	0.0887
p-value^{+}	0.0847	0.0474*	0.4724	0.0094*	

$^{+}$*p*-value for Kruskal–Wallis test comparing the values of different time periods within the group; $^{++}$*p*-value for the Friedman repeated ANOVA test comparing the values between the group at specific time; *significant *p*-value ($p \leq 0.05$)

Table 5: Comparison of ALP level in GCF between the groups at various time intervals

	Group I	*Group II*	*Group III*	*Group IV*	*p-value*$^{++}$
Baseline	61.25 ± 6.30	70.25 ± 2.19	64.44 ± 6.35	71.22 ± 7.14	0.2764
6 weeks	122.63 ± 6.19	143.00 ± 4.24	127.67 ± 18.99	157.11 ± 3.76	0.0000*
p-value^{+++}	0.0000*	0.0000*	0.0000*	0.0000*	

$^{+++}$*p*-value for Wilcoxon signed-rank test comparing the values of baseline and 6 week time periods within the group; $^{++}$*p*-value for the Friedman repeated ANOVA test comparing the values between the group at specific time; *significant *p*-value ($p \leq 0.05$

Table 6: *Post hoc* Mann–Whitney *U* test for ALP level in GCF

	Group I (OFD)	*Group II (OFD + LIPUS)*	*Group III (OFD + BG)*	*Group IV (OFD + BG + LIPUS)*
Group I (OFD)	–	0.00634*	0.26700	0.01828*
Group II (OFD + LIPUS)	0.00634*	–	0.03846*	0.09601*
Group III (OFD + BG)	0.26700	0.03846*	–	0.04744*
Group IV (OFD + BG + LIPUS)	0.01828*	0.09601	0.04744*	–

*Significant *p*-value ($p \leq 0.05$)

defect depth when compared with initial baseline measurements (2 ± 0.71 and 3.17 ± 2.93). On comparison between the groups at both time periods, there was no statistically significant difference (*p*-value > 0.05) (Table 4).

Regarding the ALP in GCF, there was a statistically significant increase in the level of ALP when compared to the baseline at 6 weeks in all the groups (*p*-value <0.001) (Table 5). Also, at 6 weeks, there were significantly high (*p*-value < 0.05) ALP levels in group II (143 ± 4.24) and group IV (157.11 ± 3.76), when compared to group I (122.63 ± 6.19) and group III (127.67 ± 18.99) (Table 6).

Discussion

In vitro studies showed that LIPUS could enhance the osteogenic differentiation of mesenchymal stem cells.[31,32] The expression of osteogenesis-related genes such as bone morphogenetic protein 2, runx2, and ALP was upregulated after LIPUS treatment.[33–35] With the background information on the potential promise of LIPUS on bone healing and regeneration, this study was executed, and results were analyzed to evaluate the effectiveness of LIPUS as an adjunct to periodontal regenerative therapy with or without BG in intrabony defects of chronic periodontitis patients.

In all the subjects, irrespective of the groups, it was apparent that the clinical assessment parameters PD and CAL were reduced significantly from baseline to 6 months. The radiographic defect depth was significantly reduced in groups II and IV from baseline to 6 months. Though there was a significant reduction in clinical and radiographic parameters at various time periods, there was no statistically significant difference between the groups at baseline, 3 or 6 months. At 6 weeks, there was a statistically significant increase in ALP level in GCF of all groups. Also, group II (OFD + LIPUS) and group IV (OFD + BG + LIPUS) showed statistically significant increases in ALP levels when compared to groups I and III.

Interestingly, there was no similar study where LIPUS was used in the regeneration of human periodontal tissue to compare our results. LIPUS has been proven to accelerate bone regeneration and fracture healing.[19–21,36] Rutten et al. performed a randomized, double-blind trial of the LIPUS effect on delayed unions[37] in osteotomized fibulas after high tibial osteotomy. He found that LIPUS could increase bone volume and mineralized volume in the area of new bone formation, and cancellous bone, respectively. A higher level of osteoid thickness and mineral apposition rate in the area of new bone formation is also reported.[38] ALP is a known biomarker for bone regeneration, as it is a membrane-bound glycoprotein produced by cells like osteoblasts during bone regeneration.[39] ALP allows bone mineralization by releasing an organic phosphate and by hydrolyzing inorganic pyrophosphate, a potent inhibitor of hydroxyapatite crystal formation and dissolution. Thus, it is found to be elevated during bone regeneration. Since it is higher during bone healing, in this study, we expected an increase in the level of ALP after periodontal therapy signifying periodontal regeneration. Similarly, in the present study, ALP level was significantly increased, implying bone formation, but the results pertaining to clinical and radiographic parameters did not significantly improve in LIPUS groups. Although LIPUS was supposed to be the only experimental factor, differences in periodontal condition or differences in remaining bone and patient's body response might have affected our results, too. Furthermore, the dosage and duration of the application of ultrasound and its effects should be explored more deeply.

In the present study, LIPUS was given on alternate days for only 2 weeks and that did not improve periodontal regeneration in terms of clinical and radiographic parameters. Nevertheless, LIPUS demonstrated an enhancing effect on ALP level stimulation at 6 weeks of postevaluation. But this positive result in biochemical level failed to translate to clinical and radiographic parameters, which were evaluated at 3 and 6 months. This may be due to the shorter duration of the application of LIPUS.

The other possible reason for such differences in the effect of LIPUS would be attributed to the smaller sample size due to the dropouts in the sample sites. The sample size was calculated with ALP level as a primary outcome instead of the clinical and radiological parameters, as there were no clinical trials with LIPUS on the human periodontium. This limitation in the present study also could be a possible reason for

not getting a clinically significant improvement in LIPUS groups in spite of having a significant improvement in ALP level in those groups. There is also a deficit in the specification of basic parameters in terms of the usage of LIPUS in human periodontal tissue regeneration due to the limited literature on this aspect. This preliminary study gives a base for future research in this field. More studies have to be performed to set a protocol for using LIPUS and further research with longer duration, and frequent application of LIPUS may exhibit a positive influence on bone regeneration. The biophysical mechanisms by which LIPUS is involved in the complex periodontal regeneration process remain unclear and require further research.

Conclusion

Low-intensity pulsed ultrasound (LIPUS), in its current dosage, did not significantly improve the periodontal regeneration in terms of clinical and radiographic parameters when used as an adjunct to OFD with or without BG in intrabony defects of chronic periodontitis patients. But it has shown the potential to increase the ALP level in GCF.

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