

Assessing the clinical efficacy of Ursodeoxycholic acid (UDCA) as a local drug delivery agent in the treatment of intra-bony defects: a clinico-radiographic study

UDCA as local drug agent in periodontitis

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Abstract

Aim & Objectives: The purpose of this clinical trial is to evaluate periodontal outcomes after local delivery of Ursodeoxycholic acid (UDCA) gel in intra-bony defects.

Patients and methods: 26 subjects participated in this study. Patients were randomly allocated into two experimental groups: the test sites received scaling and root planning (SRP) with local drug delivery of UDCA in the pocket having probing pocket depths (PPD) \geq 5mm with intra-bony defects; whereas the control sites received SRP with placebo gel. Radiographically ImageJ® analysis was used to evaluate volume of the defect fill from baseline to 6 months. Clinical parameters included recording of probing pocket depths (PPD), clinical attachment level (CAL), gingival index (GI), bleeding index (BI) at baseline, 3 months and 6 months.

Results: There was statistically no significant difference in the defect volume/fill from baseline to 6 months in the test and control groups. Significant difference was seen in reduction of PPD from baseline to 6 months; although it was not evident at 3 months. A statistically significant difference was seen in reduction of GI and BI scores with gain in CAL in the test group when compared to the control group from baseline to 3 months and 6 months.

Conclusion: The present clinical trial revealed that the anti-oxidant and anti-inflammatory properties of UDCA had an additive effect on SRP by showing improvement in the periodontal clinical parameters. It can be concluded that local drug delivery of UDCA may have an additive therapeutic effects in non-surgical periodontal therapy.

IndexTerms: Periodontitis, Ursodeoxycholic acid, Anti oxidant property, Defect volume

I. INTRODUCTION (HEADING 1)

^{II.} Periodontitis is an inflammatory condition of tooth-supporting tissues, the periodontium. One of the significant features of periodontitis, the activation of osteoclastogenesis, leads to loss of alveolar bone resulting in formation of osseous defects.^[1] Scaling and root planing is most commonly performed periodontal treatment. It has some limitations in accessing deeper pockets, root concavities, furcation areas and in removing pathogens that have infiltrated into connective tissue and dentinal tubules.^[2]

^{III.} Local drug delivery technique can maximize the efficacy of mechanical scaling and root planning in the early phase of periodontal therapy.^[3] Local drug delivery system allows for anti-microbial effect at lower dosages to produce more constant and prolonged therapeutic effect within the sub-gingival tissue of deep periodontal pockets.^[4, 5] Sustained or controlled release of the drug is the additional advantage of these local drug delivery systems.^[6]

^{IV.} Ursodeoxycholic acid (UDCA) is a natural bile acid, dissolves cholesterol gall stones and can be used for the treatment of liver diseases like primary biliary cirrhosis.^[7, 8] UDCA is identified as a non-toxic, hydrophilic bile acid.^[9] In humans it is synthesized in the large intestine from chenodeoxycholic acid and constitutes 3% of the total bile acid. The primary functions of UDCA involve digestion of lipids and cholesterol homeostasis.^[10]

^{V.} H₂O₂, one of the ROS (reactive oxygen species) considered as inveterate factor for inflammation and tissue related injury. These ROS aggravates the inflammatory response exerting harmful effects on tissue healing. UDCA is known to exert antioxidant, anti-apoptotic and anti-inflammatory effects useful for regeneration of tissue and bone. It reduces side effects related to inflammation by scavenging the overproduced H₂O₂ to increase bone regeneration in the defect sites.^[10]

^{VI.} It has been demonstrated in a mouse model that UDCA has shown anti-inflammatory effects by attenuating symptoms of rheumatoid arthritis.^[11, 12] Mast cells that are treated with UDCA reduces overproduction of cytokines and immunoglobulins from mononuclear peripheral blood cells.^[13] In beagle dogs, UDCA showed decrease in periodontal pocket depth, clinical attachment levels at 0.5 and 5% concentrations.^[14]

^{VII.} Periodontitis also is an inflammatory condition similar to hepatitis. Various *in vitro* and animal studies have showed the anti-inflammatory effects of Ursodeoxycholic acid in inflammatory mediated diseases. Therefore, the aim of this study was to assess the periodontal outcomes after local delivery of Ursodeoxycholic acid gel in intra-bony defects.

MATERIALS AND METHODS (HEADING 2)

^{VIII.} A sample size of total 26 (13 for each group) was calculated for statistical power of 0.85 , probability of error of 0.05 and effect size of 0.6. The study was conducted as a single blind, randomized controlled clinical trial, subjects were selected from the Department of Periodontology of the outpatient section.

IX. Systemically healthy male and female patients of age greater than 18 years with probing pocket depths (PPD) of ≥ 5 mm around intra-bony defects presenting with two wall or three wall defects were included. Medically compromised patients, heavy smokers, pregnant women and patients defects involving lingual sides were excluded from the study. 26 patients fulfilling the inclusion criteria were selected and all patients provided informed consent.

X. Study was approved by the ethical committee and scientific committee of the institutional review board with the approval number: SVSIDS/Perio/1/2020. The study was registered in the clinical trials with the registration number: NCT04937023.

XI. Preparation of Ursodeoxycholic acid gel and placebo gel

XII. UDCA and Phospholipids (at a ratio of 1:3 respectively) were mixed with tetrahydrofuran in a round-bottom flask (30 ml/mg of UDCA). For reaction medium tetrahydrofuran (60 ml) was used. The temperature was maintained at 40°–60°C using water bath and to a time period of 3 hours. For 10 h evaporation of tetrahydrofuran was seen under vaccum; the dried residues were then crushed in the mortar and sieved with a 100 mesh. This was added to Hydroxyethyl cellulose (HEC) polymer, prepared by combination of sodium hydroxide and cellulose further treating with ethylene oxide. For placebo gel, only hydroxyethyl cellulose polymer was used.

XIII. Outcomes

XIV. The clinical parameters were recorded after treatment at intervals of baseline, 3 and 6 months to assess the periodontal status. (1)Defect volume was assessed radiographically using radiovisiography (RVG) by Subtraction ImageJ® analysis. (2)Probing depths (3)Clinical attachment levels were assessed. (4)Gingival index (Loe H and Silness P) and bleeding index (Ainamo and Bay) scores were calculated.

XV. Interventions

XVI. Treatment Protocol

XVII. At initial appointment, the selected individuals received specific oral hygiene instructions and full mouth supragingival scaling by means of ultrasonic and hand instruments. After initial assessment and complete phase-I therapy, the patients were recalled after 1 week for examination of their oral hygiene maintenance and to collect baseline clinical data.

XVIII. In the Test Group, immediately after the SRP procedure, the prepared UDCA gel was injected into the selected sites from the base of the pocket with a blunt needle and carefully upwards to avoid air bubbles entrapment. In the Control Group, immediately after the SRP procedure, placebo gel was injected into the defect site using a blunt cannula syringe. Patients were re-examined after 3 and 6 months for recording the parameters in both groups (*Figure 1 & 2*).

XIX. Radiographically, bone regeneration was evaluated at baseline and 6 months; using commercially available image processing software (Adobe Photoshop® 6.0, Adobe Systems, San Jose, USA) the radiograph obtained at 6 months were subtracted from the radiograph taken at the initial baseline assessment. The data is then transferred to open-source software for area calculation (Image J®, Research Services Branch, NIH, Bethesda, Maryland, USA) for area calculation. (*Figure 3*)

XX. Statistical Analysis

XXI. An analysis from information of the expected outcomes in periodontitis patients was used to evaluate the effect of treatment. Statistical Package for Social Sciences (SPSS) was used for analysis of data. Repeated measures ANOVA was used to check difference in means in each group with multiple time intervals. Values of $p \leq 0.001$ were interpreted as highly significant, $p < 0.05$ were interpreted as statistically significant, , $p \geq 0.05$ as not significant and confidence intervals were at 95%.

XXII. OBSERVATIONS AND RESULTS (HEADING 3)

XXIII. This randomized clinical trial was carried out to evaluate periodontal outcomes after local delivery of Ursodeoxycholic acid gel in intra-bony defects.

XXIV. Intragroup Comparison

XXV. DEFECT VOLUME (TEST) AT DIFFERENT TIME INTERVALS

XXVI. THE DIFFERENCE IN MEAN VALUES OF DEFECT VOLUME IN THE TEST GROUP FROM BASELINE TO 6 MONTHS WAS 0.68 (0.32). ON COMPARING DEFECT VOLUME, A HIGHLY SIGNIFICANT AMOUNT OF DEFECT FILL WAS SEEN FROM BASELINE TO 6-MONTHS. ($P=0.001^{**}$) (*TABLE 1*)

XXVII. DEFECT VOLUME (CONTROL) AT DIFFERENT TIME INTERVALS

XXVIII. The difference in mean values of defect volume in the control group from baseline to 6 months was 0.52 (0.54). On comparing defect volume, a significant amount of defect fill was seen from baseline to 6-months. ($p<0.016^*$) (*Table 1*)

XXIX. PROBING POCKET DEPTHS (TEST) AT DIFFERENT TIME INTERVALS

XXX. THE MEAN VALUES (IN MM) OF PROBING POCKET DEPTHS IN THE TEST GROUP AT BASELINE, 3 MONTHS AND 6 MONTHS WERE 5.23 (0.72), 4.38 (1.12) AND 3.77 (1.30) RESPECTIVELY. ON COMPARING PROBING POCKET DEPTHS AT VARIOUS TIME INTERVALS, A SIGNIFICANT AMOUNT OF PROBING POCKET DEPTH REDUCTION WAS SEEN FROM BASELINE TO 3 MONTHS ($P=0.017^*$) AND BASELINE TO 6-MONTHS. ($P=0.05^*$)

XXXI. PROBING POCKET DEPTHS (CONTROL) AT DIFFERENT TIME INTERVALS

XXXII. The mean values (in mm) of probing pocket depths in the control group at baseline, 3 months and 6 months were 4.69 (0.85), 4.92 (0.95) and 5.15 (1.07) respectively. On comparing probing pocket depths at various time intervals, no significant difference in the amount of probing pocket depth reduction was seen from baseline to 3 months ($p=0.257$ NS) and baseline to 6 months. ($p=0.109$ NS)

XXXIII. CLINICAL ATTACHMENT LEVELS (TEST) AT DIFFERENT TIME INTERVALS

XXXIV. The mean values (in mm) of clinical attachment levels in the test group at baseline, 3 months and 6 months were 2.69 (0.48), 1.54 (0.66) and 1.08 (0.27) respectively. On comparing clinical attachment levels at various time intervals,

a significant amount of clinical attachment level gain was seen from baseline to 3 months ($p=0.002^*$) and a highly significant amount of clinical attachment level gain was seen baseline to 6- months. ($p=0.001^{**}$)

XXXV. CLINICAL ATTACHMENT LEVELS (CONTROL) AT DIFFERENT TIME INTERVALS

XXXVI. The mean values (in mm) of clinical attachment levels in the control group at baseline, 3 months and 6 months were 1.54 (0.78), 1.92 (0.64) and 2.38 (0.50) respectively. On comparing clinical attachment levels at various time intervals, a significant amount of clinical attachment level gain was seen from baseline to 3 months ($p=0.025^*$) and baseline to 6-months. ($p=0.002^*$)

XXXVII.

Intergroup Comparison

XXXVIII. Defect volume

XXXIX. There was no significant differences between the test and the control groups for the defect volume values from baseline to 6-months. ($p=0.4$ NS) (Table 1)

XL. Probing pocket depths

XLI. At baseline no significant difference was seen between the test and control groups ($p=0.105$ NS). No significant differences were observed between the test and the control groups for the probing pocket depth values from baseline to 3 months. ($p=0.218$ NS) The probing pocket depth values decreased with a statistical significance difference from baseline to 6-months ($p=0.008^*$) in the test group when compared to the control group. (Table 2)

XLII. Clinical attachment levels

XLIII. At baseline no significant difference was seen between the test and control groups ($p=0.169$ NS). Highly significant differences were observed between the test and the control groups for the clinical attachment levels from baseline to 3 months. ($p=0.001^{**}$) and from baseline to 6 months post-operatively. ($p=0.001^{**}$) (Table 3)

XLIV. Gingival index

XLV. At baseline no significant difference was seen between the test and control groups ($p=0.103$). Significant differences were observed between the test and the control groups for the gingival index scores from baseline to 3 months ($p=0.043^*$). The gingival index scores were highly significantly from baseline to 6-months ($p=0.001^{**}$) in the test group when compared to the control group. (Table 4)

XLVI. BLEEDING INDEX

XLVII. AT BASELINE NO SIGNIFICANT DIFFERENCE WAS SEEN BETWEEN THE TEST AND CONTROL GROUPS ($p=0.141$). SIGNIFICANT DIFFERENCES WERE OBSERVED BETWEEN THE TEST AND THE CONTROL GROUPS FOR THE BLEEDING INDEX SCORES FROM BASELINE TO 3 MONTHS. ($p=0.02^*$) FROM BASELINE TO 6-MONTHS POST-OPERATIVE INTERVALS THE BLEEDING INDEX SCORES WAS HIGHLY SIGNIFICANT BETWEEN IN THE TEST GROUP WHEN COMPARED TO THE CONTROL GROUP. ($p=0.001^{**}$) (TABLE 5)

XLVIII. DISCUSSION (HEADING 4)

XLIX. Local drug delivery is a treatment modality which consists of administration antimicrobial agents in the periodontal pockets with bio degradable sustained or controlled release. The concept was proposed by Goodson et al., in 1979.^[16] Since then, many studies have used this form of therapy using various materials and vehicles to deliver the drugs as an adjunct to scaling and root planing with prominent results in clinical parameters.

L. UDCA has anti-inflammatory and antioxidant properties that are helpful in decrease or resolution of inflammatory disease conditions.^[10] It is widely accepted that overproduced inflammation related cytokines are key factors for progression of periodontitis. Thus, it is important to reduce the cytokines overproduction to control the inflammatory disease.^[16] Various studies showed that the UDCA effectively inhibited the release of these inflammatory cytokines.

LI. A study by Song et al.,^[17] studied the anti-inflammatory response of UDCA on human acute monocytic leukemia cell line (THP-1) cultured by Aggregatibacter actinomycetemcomitans. Results of this study suggested that pretreatment with UDCA successfully decreased the A. actinomycetemcomitans mediated IL-17A, TNF- α and IL-1 β production in a dose related manner.

LII. An in-vitro study provided information supporting anti-inflammatory effects of UDCA on human gingival fibroblasts, in reducing the cytokines levels like TNF- α and IL-1 β , also the reduction of IL-6 release by oral human squamous carcinoma cell (HCS-2) cells.^[18]

LIII. The present *in vivo* randomized clinical study was done to assess the periodontal outcomes after local drug delivery of Ursodeoxycholic acid gel in intra-bony defects. On intragroup comparison of defect fill in test group, the mean difference values for defect volume in the test group from baseline to 6 months was 0.68. A highly statistical significance for defect fill was seen in the test group ($p<0.001^{**}$)

LIV. The present study results was in par with other study conducted by Yoshiie Arai et.al.,^[10] where the potential of pro drug UDCA nanoparticles in a rat model for bone regeneration in long bones was evaluated. Significant increase in the trabecular thickness was seen in the UDCA group upto 1.42 times higher than that of the control group, whereas in the present study 0.68 mm of defect fill was seen after 6 months.

LV. The highly significant value for defect fill in test group could be due to anti-oxidant property of UDCA. The oxidative properties of reactive oxygen species (H_2O_2) is the reason for damage to the tissues and delaying in regeneration at defective sites. Elevated ROS levels relay the apoptotic signals to the cells, increasing adipogenic differentiation, and decreasing the potential osteogenic differentiation of mesenchymal stem cells. Thus, reducing the H_2O_2 enhance the bone regenerative property of UDCA.^[10]

LVI. On intergroup comparison of defect fill, though numerically test group revealed more defect fill when compared to the control, this difference between the two groups was not statistically significant from baseline to 6 months. ($p=0.4$ NS) This suggests that addition of UDCA to SRP had similar effects to that of SRP alone. This could be due to lack of sustained release of

UDCA. A study **Yoshie Arai et.al.**,^[10] suggested that sustained release of UDCA was seen in prodrug of UDCA as nanoparticles (PUDCA) and this form had superior bone regeneration than the plain UDCA.

LVII. The probing pocket depth and gingival index values decreased with a statistical significance difference from baseline to 6-months in the test group when compared to the control group. The mean reduction in PD was higher in our study when compared to control, which may be due to the local drug delivery of UDCA.

LVIII. These results were in line with a study conducted by **Park et al.**,^[14] to assess the effect of UDCA at different concentrations against control group for clinical parameters in beagle dogs in ligature induced periodontitis. In this animal study, results showed significant decrease in pocket depth and ginvival index after 8 weeks, which was similar to present study with decrease in gingival index in 3 months. however, no pocket depth reduction was recorded at 12 weeks interval, though a significant difference was recorded after 24 weeks (6 months).

LIX.

LX. LIMITATIONS

LXI. The present study has certain limitations that need to be contemplated to interpret the results. The present study is a short-term clinical study and in long-term clinical studies drug feasibility have to be investigated. GCF collection for drug release at various time intervals was not assessed in the present study. The microbiological parameters were not evaluated. The efficacy of UDCA in different forms of local drug delivery systems also should be evaluated.

LXII. Although, significant defect fill was not seen, improvement in clinical parameters was seen by local drug delivery of UDCA. Future studies with different concentrations of UDCA and measured kinetics of local drug release may help in the treatment of initial stages of periodontitis and even peri-implantitis.

LXIII. CONCLUSION (HEADING 5)

LXIV. A comparative clinical study was performed to assess the periodontal outcomes after local delivery of Ursodeoxycholic acid gel in intra-bony defects. Improvement in clinical parameters seems to imply that the local delivery of Ursodeoxycholic acid gel as an adjunct to non-surgical periodontal therapy in the treatment of periodontitis can enhance the potential benefits of scaling and root planing.

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TABLES

Table 1: Test group - defect volume values intragroup and intergroup comparison

Groups	N	Baseline to 6 months	U- value	p-value
Test	13	0.68±0.32	54	0.001**
Control	13	0.52±0.54	122	0.016*
(p-value)		0.4 (NS)		

Mannwhitney u test $P<0.05^*$ (significant); $p>0.05^†$ (non-significant); $p \leq 0.001^{**}$ (highly significant)

TABLE 2: INTERGROUP COMPARISON OF PROBING POCKET DEPTHS

Intervals	Group	N	Mean	SD	U-value	p-value
Baseline	Test group	13	5.23	0.72	55	0.105(NS)
	Control group	13	4.69	0.85		

3-months	Test group	13	4.38	1.12	62.5	0.218(NS)
	Control group	13	4.92	0.95		
6-months	Test group	13	3.77	1.30	34.5	0.008*
	Control group	13	5.15	1.07		

Mannwhitney u test; $p<0.05^*$ (significant); $p>0.05^†$ (non-significant); $p\leq0.001^{**}$ (highly significant)

TABLE 3: INTERGROUP COMPARISON OF CLINICAL ATTACHMENT LEVELS

Intervals	Group	N	Mean	SD	U-value	p-value
Baseline	Test group	13	2.69	0.48	23	0.169(NS)
	Control group	13	1.54	0.78		
3-months	Test group	13	1.54	0.66	57.50	0.001**
	Control group	13	1.92	0.64		
6-months	Test group	13	1.08	0.27	4	0.001**
	Control group	13	2.38	0.50		

Mannwhitney u test; $p<0.05^*$ (significant); $p>0.05^†$ (non-significant); $p\leq0.001^{**}$ (highly significant)

TABLE 4: INTERGROUP COMPARISON OF GINGIVAL INDEX (GI)

Intervals	Group	N	Mean	SD	U-value	p-value
Baseline	Test group	13	1.84	0.55	43.5	0.103(NS)
	Control group	13	1.31	0.48		
3-months	Test group	13	1.15	0.37	52.0	0.043*
	Control group	13	1.53	0.51		
6-months	Test group	13	0.77	0.72	18.0	0.001**
	Control group	13	2.07	0.64		

Mannwhitney u test; $p<0.05^*$ (significant); $p>0.05^†$ (non-significant); $p\leq0.001^{**}$ (highly significant)

TABLE 5: INTERGROUP COMPARISON OF BLEEDING INDEX (BI)

Intervals	Gingival bleeding index	N	Test	Control	U- value	P - value
Baseline	Negative	13	2(15.4%)	0(0)	2.17	0.141(NS)
	Positive	13	11(84.6%)	13(100)		
3 months	Negative	13	11(84.6%)	5(38.5)	5.85	0.02*

	Positive	13	2(15.4%)	8(61.5)		
6 months	Negative	13	12(92.3%)	8(61.5)	3.67	0.001**
	Positive	13	1(7.7%)	5(38.5)		

Mannwhitney u test; $p<0.05^*$ (significant); $p>0.05^{†}$ (non-significant); $p\leq0.001^{**}$ (highly significant)

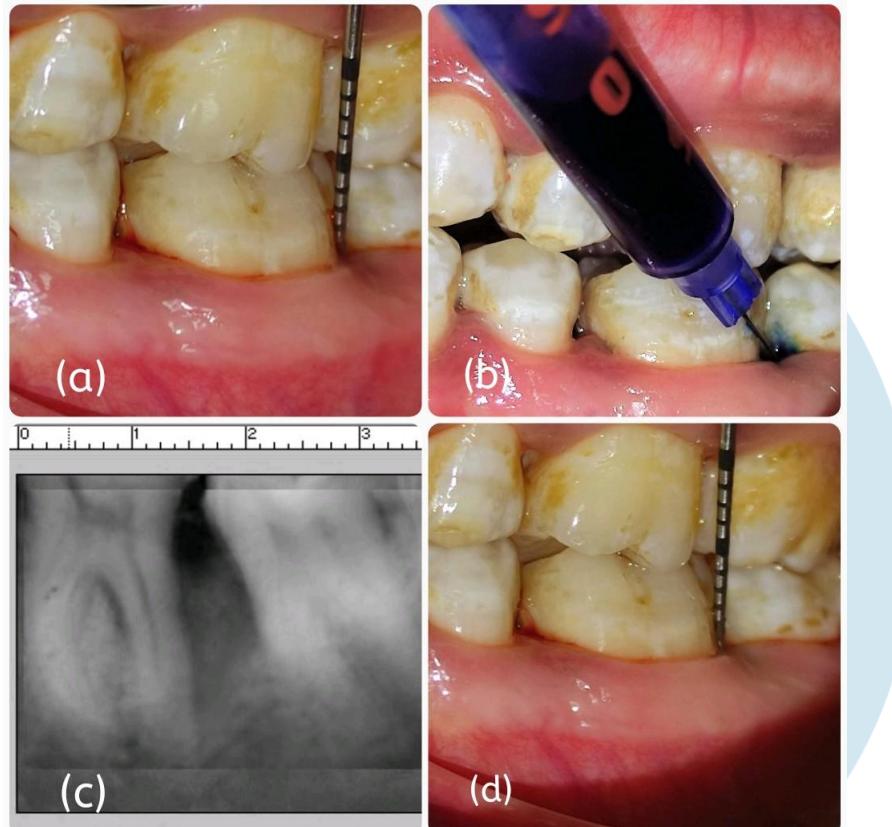


Figure 1: (a) pre-op probing pocket depth; (b) UDCA gel placed into test site; (c); (d) intra bony defect at test site; (e) 6 months post-op PPD

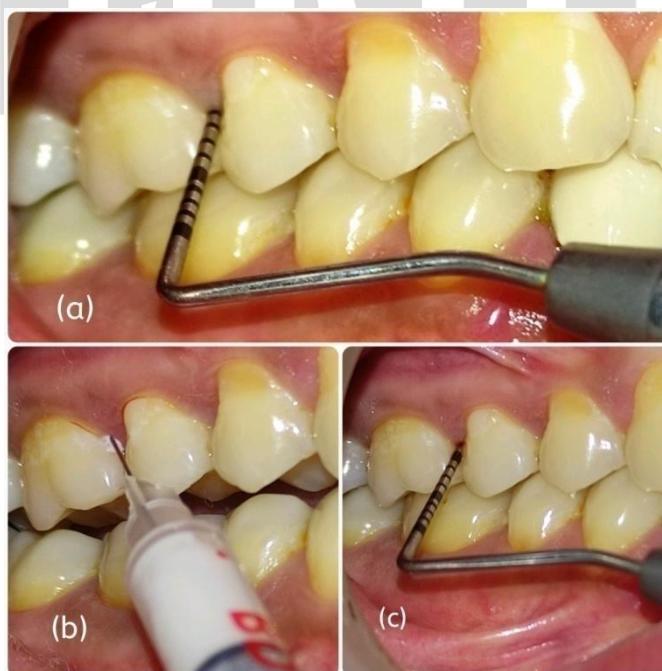


Figure 2: (a) pre-op probing pocket depth; (b) Placebo gel placed into test site;

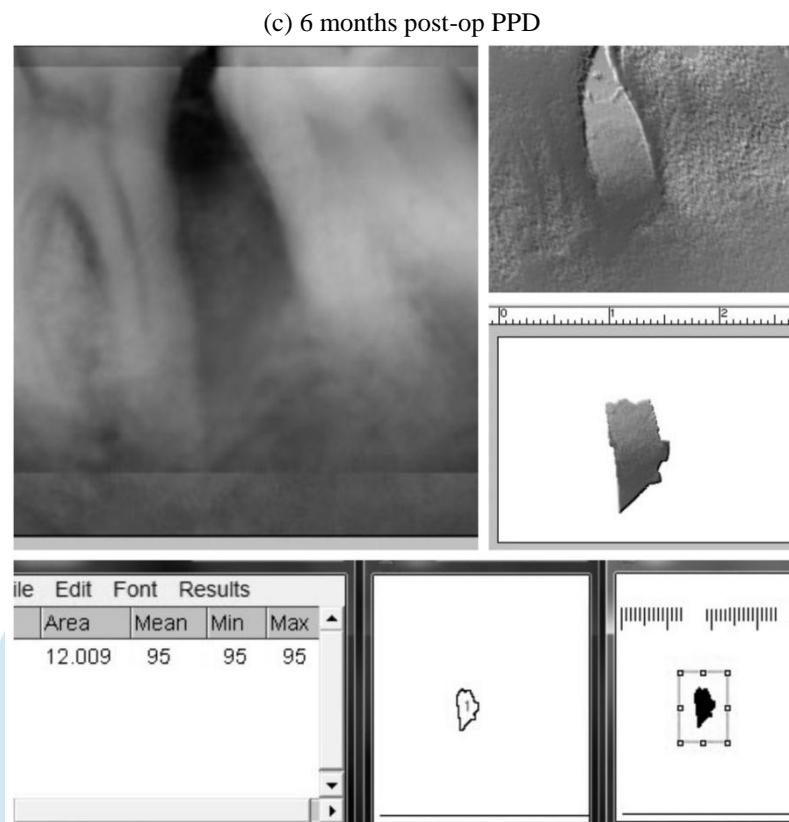


FIGURE 3: The initial radiographic image obtained at baseline (top-left) was subtracted from the radiographic images taken at 3 or 6-months (top-right), in Adobe Photoshop® 6.0. The obtained layer (bottom-left) was transferred into Image J® software for area calculation (bottom-right).

LXV. ACKNOWLEDGMENT

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