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Original Research

Simvastatin Collagen Graft In the surgical management of Mandibular Class II Furcation Defects

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ABSTRACT

Background: The management of multi-rooted teeth affected by periodontal disease has remained a challenge. Local application of Simvastatin stimulates bone formation by expression of Bone morphogenetic protein-2 and also promotes periodontal healing. The present study evaluates the benefits of 'Simvastatin collagen graft' in comparison to 'collagen graft' in the surgical management of class II furcation involved teeth.

Materials and Methods: Employing a split mouth design, a total of 40 bilateral mandibular class II furcation defects in 20 systemically healthy subjects were randomized as test and control sites. Simvastatin collagen graft was placed in the test sites and collagen graft was placed in the control sites. Clinical parameters including site specific plaque index, gingival index, bleeding index, probing depth and clinical attachment level were recorded at baseline, 6 months, 9 months 12 months and 15 months. Radiographic assessment of bone fill was made using standardized intraoral periapical radiographs with an X- ray mesh gauge taken at baseline, 6, 9, 12 and 15 months. The results were analyzed statistically.

Results: A statistically significant decrease in probing pocket depth and improved clinical attachment level was observed in both groups over 15 months, but comparisons between the test and control groups did not show statistically significant differences. Radiographic analysis showed bone formation. The percentage bone area between the test and control over 15 months showed statistically significant differences.

Conclusion: Simvastatin collagen graft and collagen graft both showed improvements in clinical parameters and evidence of bone formation. The results encourage the adjunctive use of Simvastatin collagen graft for predictable regeneration of grade II furcation defects.

INTRODUCTION

Periodontitis is an infection mediated destruction of the alveolar bone and soft tissue attachment to the tooth. It is influenced by host response, genetic susceptibility and other risk factors.[1] the invasion of the furcation areas of multi-rooted teeth with periodontitis causes progressive loss of connective tissue attachment and alveolar bone resorption. Due to anatomic limitations, furcations prevent adequate plaque control and intervention which may result in tooth loss eventually.[2] Many treatment modalities has been used to treat and improve prognosis of class II furcation defects. Although, open flap debridement yields effective calculus removal, adjunctive use of different bone grafts and membranes are found to benefit periodontal regeneration in furcation involved teeth.[3]

Statins are inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase enzyme in mevalonate pathway of cholesterol synthesis, and hence used in treatment of hyperlipidemia. Simvastatin is a

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synthetic which on local application was found to stimulate bone morphogenetic protein -2 (BMP-2) expression and stimulate bone formation.[4] They also suppress osteoclast activity in bone healing sites and exert anti-resorptive effect. The biologically significant anti-inflammatory and anti-oxidant effects facilitate periodontal healing.[5]

Periodontitis patients on systemic statin therapy were found to have lesser periodontal pockets.[6] Local delivery of Simvastatin gel in periodontal pocket sites was associated with reduced probing pocket depth, improved clinical attachment and significant bone fill.[7] Similar results were seen in study involving local delivery of Simvastatin gel in grade II furcation defects.[8] Statin contained in Collagen type I sponge was used in rabbit bone and found osteoinductive activity with BMP-2 expression.[9]

The present study was conceptualized to evaluate the efficacy of Simvastatin impregnated in collagen sponge by placing it in grade II furcation defects after open flap debridement in comparison to collagen sponge alone placed in the contra lateral furcation defect. The clinical and radiographic assessment was done over a period of 15 months.

Materials and methods

Trial design: This was a controlled, interventional study with split mouth design. It was a single centered prospective study of 15 months duration.

Participants: The study was conducted at the Department of Periodontology, J.S.S. Dental College and Hospital, a constituent college of JSS university, Mysore, India from February 2011 to November 2012. The study protocol was approved by the Institutional Review Board, JSS Dental College and Hospital, an affiliated institution of the JSS university, Mysore. The investigation was performed in accordance to the requirements of the "Declaration of Helsinki" as was adopted by the 18thWorld Medical assembly in 1964 and revised in Edinburgh in 2000.

Sampling: Patient enrolment was conducted by a study examiner[¶] by purposive sampling from the outpatients presenting to the department of Periodontology. Patients were explained the elected procedure in detail and included for the study with their written consent.

Patient's eligibility: Twenty systemically healthy subjects both men and women within the age group 45-55 years were included in the study. The presence of two contra lateral sites with with Class II furcation involvement was necessary for intervention. Only vital teeth, as revealed by a positive cold test, were included in the study. Subjects in good systemic health, with no inflammatory, infectious, immune or hormonal anomalies were included. Smokers, pregnant and lactating women, patients on systemic statin therapy or those with confirmed allergy to the material were excluded.

Initial therapy: Scaling and root planing of the selected teeth in the planned quadrant was performed using ultrasonic device and hand curettes under local anesthesia. Patients were re-evaluated after 6 weeks of initial therapy and scheduled for intervention based on presence of two similar contra lateral defects (Hamp's defect, horizontal loss of periodontal support ≥3mm but ≤7mm) and plaque index and gingival index less than 1.

Randomization and Intervention: The selected sites i.e. two contra lateral sites with class II furcation involvement in each individual were randomized using toss of a coin. The sites were assigned as test site (Simvastatin collagen graft) and control site(collagen graft) by the study therapist [ǂ].

Outcome Measures: The clinical parameters were measured at 6-, 9-, 12 and 15-month intervals were the change in PI; GI; reduction in PD; gain in clinical

attachment level (CAL). The radiographic parameter assessed was the percentage bone fill at 6, 9, 12 and 15 months in the postoperative period.

Calibration of the study examiner: The clinical measurements were performed by a single therapist[¶] other than the study therapist[ǂ]. Five patients, each with 2 pairs of contra lateral teeth (single and multi-rooted) with probing depths >4 mm on at least one aspect of each tooth, were used for intra examiner calibration. The examiner evaluated the patients on 3 separate occasions 24 hours apart. Calibration was accepted if measurements at baseline, 48 and 72 hours were similar to the millimeter at a >90% level.

Presurgical Clinical Measurements: Plaque Index (Tureskey modification of Quigley Hein index),[10] Gingival Index (Loe and Silness),[11] and sulcus bleeding index (Muhlemann and Son)[12] were measured. The Probing depth and clinical attachment level were measured by a manual periodontal probe[ſ] using customized acrylic stents.[13] Horizontal Probing depth at the furcation using 2N Naber's probe.

Radiographic assessment: Conventional intraoral periapical radiographs (IOPAR) with X ray mesh gauge(grid) were taken at baseline and repeated at 6 months, 9 months, 12 months and 15 months from baseline by the study examiner[¶] the height, width and area of bone fill was assessed using a computer aided software.[†](figure 3)

Procedure Of Graft Formulation: 1.2 grams of Simvastatin powder was weighed on a weigh scale. It was added to 100ml solvent i.e. biologic grade ethanol and stirred until the powder completely dissolved to form a clear solution. The solution thus obtained had a concentration of 12mg/ml (1.2 mg/0.1 ml). The solution was transferred into a sterile dark glass bottle and closed to obtain a tight seal. The solution was stored in the refrigerator at 4^0 centigrade. The Simvastatin collagen graft was prepared 15 minutes prior to its placement in the defect site. Sterile collagen sponge 10 mm X 10 mm[¥] was placed in a sterile dappen dish. From the previously prepared Simvastatin solution, 0.1 ml of Simvastatin solution (containing 1.2mg Simvastatin) was loaded into a sterile disposable syringe and impregnated onto the Collagen sponge to form Simvastatin collagen graft.

Surgical Procedures: A local infiltration of 2% lidocaine containing epinephrine at a concentration of 1:100,000 was made followed by buccal and lingual sulcular incisions, and mucoperiosteal flaps were elevated. After flap reflection and complete debridement, collagen graft was placed in the control site and statin collagen graft was placed in the test site (Fig. 2). Interrupted sutures using 4-0 silk sutures were placed to reposition the flaps, and a periodontal dressing was placed over the surgical area. Postoperative instructions, antibiotics and oral analgesics were prescribed. One week postoperatively, periodontal dressing and silk sutures were removed. Patients were examined at 1-week, 2-week, and 1-month intervals after the surgeries and then at 6, 9, and 12 months.

Statistical analysis

The values obtained from clinical evaluation were tabulated and subjected to statistical analysis using statistical software[ſ]. Pearson's correlation co efficient and Kappa analysis were used to assess the intra examiner calibration. The descriptive statistics and repeated measure ANOVA test was employed to assess the changes in the clinical parameters at various intervals. The paired "t-test" was used for intra group comparisons over the durations. The independent samples "t" test was used for inter group comparisons over the durations. Any value < 0.05 was considered statistically significant.

Results

The number of subjects analyzed and the drop outs are presented in the consort flowchart (Figure 1).on clinical examination no inflammation or erythema in the test sites was observed one week post operatively and no patient reported with discomfort. A statistically significant ($p < 0.05$) decrease in the site specific plaque index, bleeding index, probing depth, vertical bone probing depth, horizontal bone probing depth and a significant gain in clinical attachment level was found in test sites and control from baseline over 15 months(Table 1). On inter group comparisons, statistically significant difference in bleeding index and horizontal bone probing depth from base line to 15 months interval was observed. But the differences in other clinical parameters were insignificant (table 2). There was radiographic evidence of bone fill in the furcations measured as increments in bone area in both test and control sites. But statistically significant increase in bone area was seen in test group ($p< 0.05$) over 15 months (table 2).

Discussion

The morphologic characteristics of a molar furcation and the resultant periodontal lesion are the most influential factors for the unpredictable success of molar furcation therapy.[14] several studies have reported that molar teeth with furcation involvement were the most frequently lost teeth. First molars have shorter root trunks than second molars which accounts for their having a higher prevalence of furcation involvement.[3] Owing to the complex anatomy and small entrance, furcation areas offer limited access to effective periodontal instrumentation.[15] Various non surgical and surgical therapies have been attempted in managing the furcation problem. Some studies have shown encouraging results with the use of allogenic bone grafts and barrier membranes.[16] Topical delivery of biological molecules like BMP-2 has shown enhanced bone growth but is associated with rapid degradation at treatment site and can elicit immune response.[17] local application of Simvastatin in different carriers in various animal models has demonstrated bone formation by up regulation of BMP-2.[18] 1.2 mg Simvastatin gel delivered subgingivally in human class II furcation defects has demonstrated significant clinical improvement.[8] Some studies have concluded collagen to be a suitable delivery vehicle for Statins. An animal study conducted on parietal bone of rabbits compared the amount of new bone produced by statin collagen graft and that produced by collagen grafts alone. The investigators found that Statin collagen grafts produced more new bone than collagen graft alone. They concluded that statin collagen grafts were osteoinductive and can be potentially used as bone graft material.[19] Thus, this study was formulated to evaluate the efficacy of 1.2 mg Simvastatin collagen graft in mandibular molars with class II furcation defects in comparison to collagen graft. The study used a surgical approach as it yields better calculus removal and better access for proper placement of the graft.[20]

This was a study incorporating 20 subjects (6 males and 14 females) with an average age around 36 years. The study included 40 sites with class II furcation defects which were randomized based on the guidelines for testing new materials against. This is done by treating two similar lesions in the same patient identically except for the material under investigation, with each of the treatments randomly selected and evaluated identically to avoid intrapatient variations.[21]

A statistically significant reduction in Probing depth, clinical attachment level, horizontal and vertical bone probing depth over 15 months period was observed in both test and control groups. The results are similar to that of the study with local delivery of Simvastatin gel in class II furcation areas.[8] A previous randomized

controlled study confirmed the anti-inflammatory effects of subgingival delivery of 1.2 mg Simvastatin gel in chronic periodontitis. They found significant improvements in clinical parameters like probing depth and clinical attachment level. The study also showed radiographic evidence of bone fill.[7]A similar study showed the beneficial effects of subgingivally delivered Simvastatin in type II diabetic patients with Chronic periodontitis. A significant reduction in bleeding index, probing depth and a significant gain in attachment was observed.[22]

Simvastatin collagen graft was compared with collagen sponge alone in order to test the efficacy of Simvastatin. In the present study, mean area percentage bone fill of 173% at test site as compared to 61% in control site was observed. The comparison was statistically significant. A previous animal study conducted on parietal bone of rabbits found that statin collagen grafts produced 308% more new bone than absorbable collagen alone.[19]

No adverse reactions were reported in any furcation site treated with Simvastatin. This is justified by the fact that systemic Simvastatin is well tolerated. Also, various studies have tested the safety profile of locally applied simvastatin.[23, 8]

Clinical implications: Simvastatin collagen graft has the potential to affect bone growth by increasing BMP-2 locally, thus can be used as an safe and cost effective alternative to topical application of expensive biologic molecules like growth factors and BMP-2 without the risk of degradation and adverse immune response. Simvastatin also exhibits anti inflammatory and antioxidant properties which can benefit periodontal tissue healing.

Limitations: The study was done in a single centre involving 20 subjects, a multicentre study with larger sample size would be more imperative. Since Simvastatin may be influenced by a range of factors including the method of administration, duration of exposure and bioavailability, further research is needed to determine the optimal therapeutic threshold, mode of application and the effectiveness for humans for bone regeneration.

Conclusion

This is a preliminary study attempting the surgical management of grade II furcations using Simvastatin collagen graft in humans. The positive results prompt its use in larger research studies and in clinical setups as a safe and cost effective adjunctive to surgical debridement for more predictable management of furcation involved teeth.

Table 1: Mean values of clinical parameters at various time intervals

Group	PI	GI	BI	PD	CAL	V-PD	H-PD	Bone area
TEST								
N= 20								
Baseline	0.40±0.24	0.42±0.25	0.36±0.27	2.60±0.50	2.80±0.61	3.25±0.44	2.85±0.58	2.83±1.33
6 months	0.35±0.12	0.37±0.15	0.36±0.12	1.95±0.39	2.25±0.63	2.40±0.50	2.05±0.22	3.19±1.41
9 months	0.20±0.10	0.31±0.22	0.18±0.13	1.80±0.41	1.90±0.30	1.95±0.39	1.90±0.44	3.54±1.63
12 months	0.33±0.16	0.30±0.17	0.23±0.19	1.75±0.44	1.90±0.55	1.55±0.51	1.45±0.60	3.85±1.55
15 months	0.23±0.17	0.28±0.19	0.08±0.12	1.15±0.36	1.50±0.51	1.25±0.55	1.40±0.59	4.44±1.94
p value	0.002	0.024	0.000	0.000	0.000	0.000	0.000	0.022
CONTROL								
N=20								
Baseline	0.36±0.15	0.48±0.23	0.27±0.18	2.65±0.58	2.90±0.64	3.05±0.60	3.10±0.30	2.29±0.96
6 months	0.21±0.23	0.25±0.25	0.16±0.16	2.25±0.55	2.60±0.50	2.30±0.47	2.40±0.50	2.28±0.69
9 months	0.25±0.19	0.30±0.31	0.23±0.19	1.80±0.61	2.50±2.32	2.00±0.56	1.95±0.22	2.44±0.77
12 months	0.23±0.05	0.41±0.28	0.18±0.11	1.75±0.44	1.70±0.47	1.70±0.47	1.80±0.41	2.67±0.86
15 months	0.23±0.15	0.31±0.21	0.16±0.17	1.30±0.47	1.40±0.50	1.40±0.50	1.85±0.48	2.69±0.93
p value	0.053	0.037	0.038	0.000	0.000	0.000	0.000	0.363

PI- Plaque Index; GI- Gingival Index; BI- Bleeding Index; PD- Probing Depth; CAL- Clinical attachment level; H-PD- Horizontal bone probing depth; V-PD- Vertical bone probing depth.

Bone area- Mean values of bone area at the furcation at various time intervals

N- Number of sites. *P≤0.05 was considered statistically significant.*

Table 2: Inter Group comparisons of mean values of clinical parameters at various time intervals

Parameter	Test	Control	p value
PI			
Baseline	0.40±0.24	0.36±0.15	0.568
6 months	0.35±0.12	0.21±0.23	0.026
9 months	0.20±0.10	0.25±0.19	0.324
12 months	0.33±0.16	0.23±0.05	0.016
15 months	0.23±0.17	0.23±0.15	1.000
GI			
Baseline	0.42±0.25	0.48±0.23	0.429
6 months	0.37±0.15	0.25±0.25	0.068
9 months	0.31±0.22	0.30±0.31	0.885
12 months	0.30±0.17	0.41±0.28	0.139
15 months	0.28±0.19	0.31±0.21	0.247
BI			
Baseline	0.36±0.27	0.27±0.18	0.241
6 months	0.36±0.12	0.16±0.16	0.001
9 months	0.18±0.13	0.23±0.19	0.346
12 months	0.23±0.19	0.18±0.11	0.316
15 months	0.08±0.12	0.16±0.17	0.023
PD			
Baseline	2.60±0.50	2.65±0.58	0.774
6 months	1.95±0.39	2.25±0.55	0.055
9 months	1.80±0.41	1.80±0.61	1.000
12 months	1.75±0.44	1.75±0.44	1.000
15 months	1.15±0.36	1.30±0.47	0.267
CAL			
Baseline	2.80±0.61	2.90±0.64	0.618
6 months	2.25±0.63	2.60±0.50	0.062
9 months	1.90±0.30	2.50±2.32	0.260
12 months	1.90±0.55	1.70±0.47	0.225
15 months	1.50±0.51	1.40±0.50	0.537
V-PD			
Baseline	3.25±0.44	3.05±0.60	0.241
6 months	2.05±0.22	2.30±0.47	0.520

9 months	1.95±0.39	2.00±0.56	0.746
12 months	1.55±0.51	1.70±0.47	0.340
15 months	1.25±0.55	1.40 ±0.50	0.374
H-PD			
Baseline	2.85±0.58	3.10±0.30	0.100
6 months	2.05±0.22	2.40±0.50	0.007
9 months	1.90±0.44	1.95±0.22	0.657
12 months	1.45±0.60	1.80±0.41	0.039
15 months	1.40±0.59	1.85±0.48	0.013
Bone area			
Baseline	2.83±1.33	2.29±0.96	0.151
6 months	3.19±1.41	2.28±0.69	0.013
9 months	3.54±1.63	2.44±0.77	0.010
12 months	3.85±1.55	2.67±0.86	0.005
15 months	4.44±1.94	2.69±0.93	0.001

PI- Plaque Index; GI- Gingival Index; BI- Bleeding Index; PD- Probing Depth; CAL- Clinical attachment level; H-PD- Horizontal bone probing depth; V-PD- Vertical bone probing depth. Bone area- Mean values of bone area at the furcation at various time intervals

P≤0.05 was considered statistically significant.

Symbols

¶ : Gauresh Kumar Patel

ǂ : Shivali S Gaekwad

ʃ : University of North Carolina-15 (UNC 15) probe

† : AutoCAD

¥ : Kolaspon®, Eucare Pharmaceutics

ƒ : SPSS for Windows version 16.0 and Minitab version 11.0 for windows.

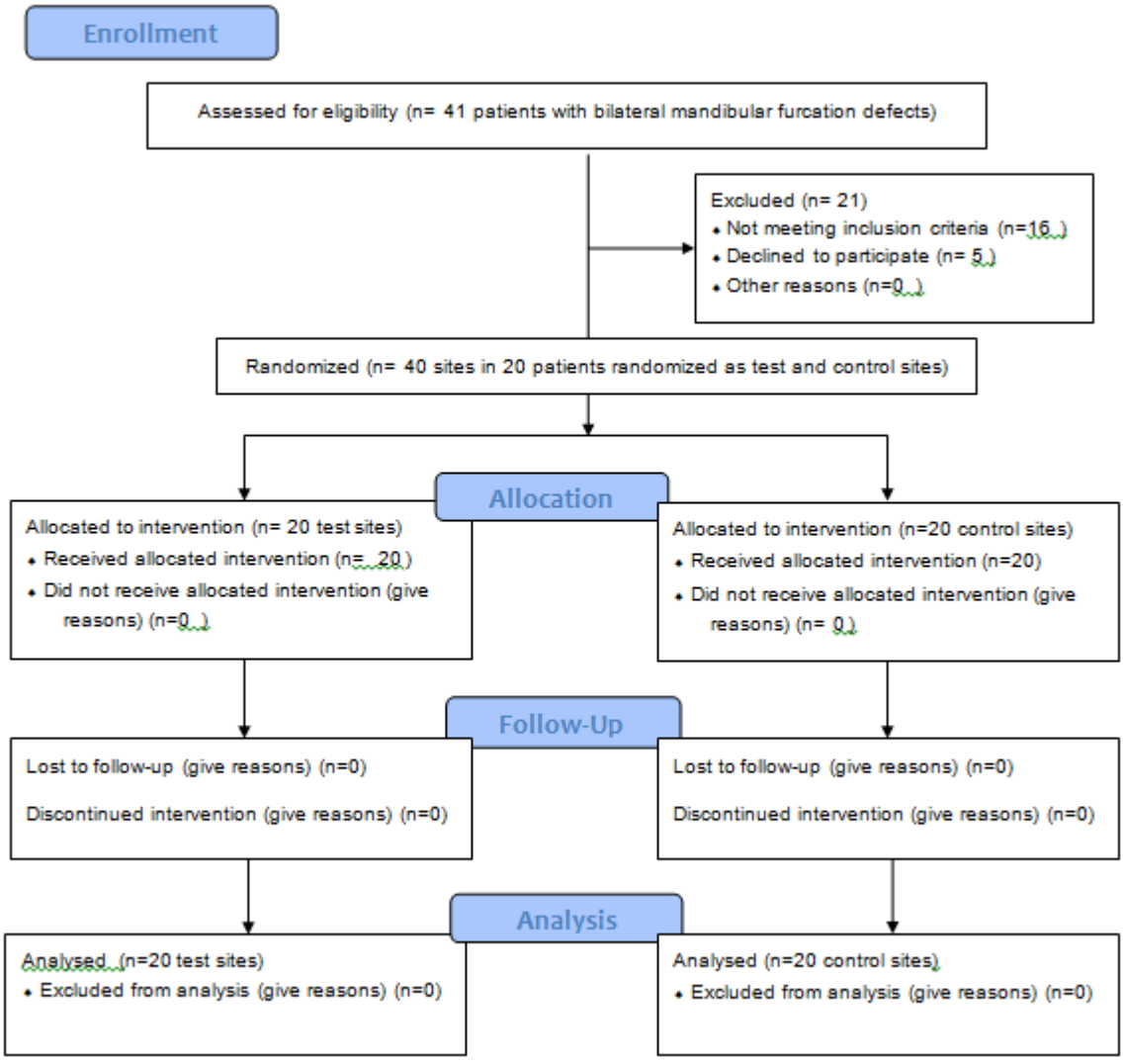
Enrollment
Assessed for eligibility (n= 41 patients with bilateral mandibular furcation defects)
Excluded (n= 21)
• Not meeting inclusion criteria (n=16)
• Declined to participate (n= 5)
• Other reasons (n=0)
Randomized (n= 40 sites in 20 patients randomized as test and control sites)
Allocation
Allocated to intervention (n= 20 test sites)
• Received allocated intervention (n= 20)
• Did not receive allocated intervention (give reasons) (n=0)
Allocated to intervention (n=20 control sites)
• Received allocated intervention (n=20)
• Did not receive allocated intervention (give reasons) (n= 0)
Follow-Up
Lost to follow-up (give reasons) (n=0)
Discontinued intervention (give reasons) (n=0)
Lost to follow-up (give reasons) (n=0)
Discontinued intervention (give reasons) (n=0)
Analysis
Analysed (n=20 test sites)
• Excluded from analysis (give reasons) (n=0)
Analysed (n=20 control sites)
• Excluded from analysis (give reasons) (n=0)

Figure 1: Consort flow chart for patient enrollment, allocation, follow up and analysis

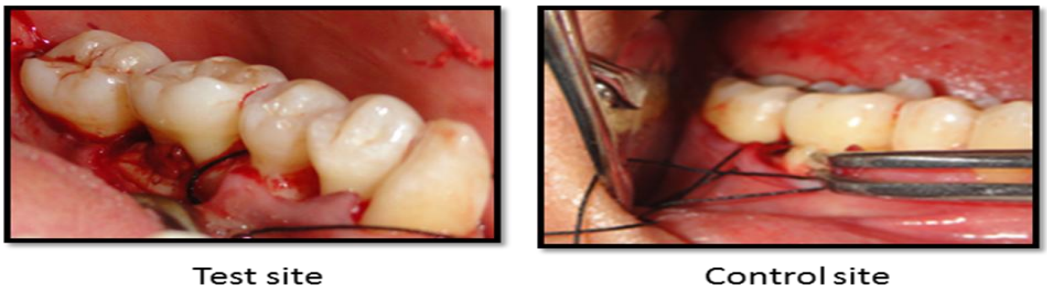

Figure 2: Placement of Simvastatin collagen graft in test site and collagen graft in control site

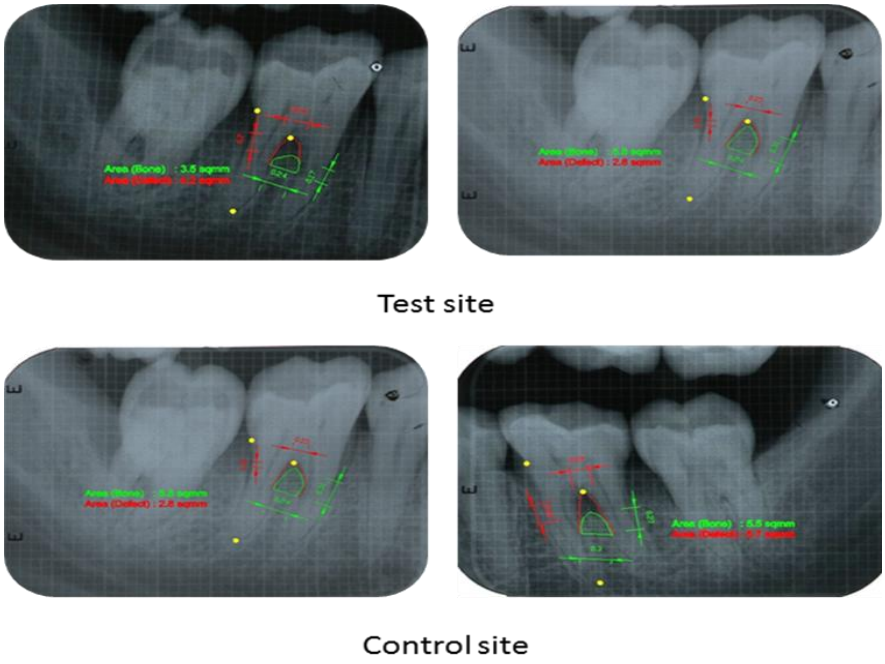

Figure 3: Comparison of bone fill between baseline to 15 months in test and control sites

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