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REOSSEOINTEGRATION OF BONE DEFECT SURROUNDING DENTAL IMPLANT ASSOCIATED WITH PERIIMPLANTITIS USING NANOBONE WITH OR WITHOUT SIMVASTATIN: A SIX MONTH RANDOMISED CONTROLLED CLINICAL TRIAL

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ABSTRACT

Objectives: The aim of the study was evaluating the effect of adding simvastatin to synthetic bone substitute on the regenerative surgical treatment of bone defects associated with periimplantitis in a six months randomized controlled clinical trial.

Material & Methods: 30 patients diagnosed with periimplantitis divided in two groups, group I treated by using synthetic bone substitute (Nanobone), group II treated by using Nanobone with simvastatin. Clinical evaluation was the measurements for probing pocket depth (PPD), clinical attachment level (CAL), plaque index (PI), modified sulcus bleeding index (mSBI) and mucosal recession. Radiographic bone fill was evaluated at baseline and after six months.

Results: The results for both treatment groups showed significant reductions obtained in the mean PPD, CAL and mSBI at six months postoperatively when compared to baseline values, on the other-side no statistically significant difference was observed for the mean PI and MR. The mean of bon fill in group II was better than that of group I and this results was statistically significant ($P < 0.05$).

Conclusions: The two regenerative approaches produced significant improvements in both clinical and radiographic assessments, but adding simvastatin to Nanobone produce better results in terms of bone fill.

KEYWORDS: Nanobone, simvastatin, periimplantitis, surgical treatment.

INTRODUCTION

Periimplantitis is pathological disease characterised by irreversible bone loss surrounding dental implant, bleeding on probing (BoP), suppuration with or without concomitant increasing of periimplant pocket [1]. Recent systematic review showed 22% prevalence rate of periimplantitis [2]. Periodontitis and periimplantitis have a similar pathogenesis, this advocate similar management

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approaches[3,4], but inflammatory infiltration in the apical extension is more pronounced in periimplantitis than in periodontitis, suggesting that periimplantitis progress faster than periodontitis[4,5]. The main goals of periimplantitis management are preserving the implant supporting tissue by the decontamination of exposed implant surfaces to inflammation resolution achievement [6]. Nonsurgical treatment has limited effect for moderate and sever periimplantitis, therefore surgical access required to improve cleans-ability of the implant surface and periimplant bone defect reconstruction [7]. There are many treatment protocols documented for achieving variable success [8–11].

Regenerative surgical treatment of periimplantitis result in probing pocket depth reduction and bone defect fill [12-14].

Nanotechnology used in periodontal tissue regeneration, there are several studies demonstrated the significance effect of nanoscale geometry and topography on the cell differentiation and regeneration[15]. Nanobone (Artoss co, Germany) consisted of synthetic nano crystalline hydroxyapatite and silica fabricated in a sol/gel process. Based on the more recent results, Nanobone increase osteoblasts proliferation better than DBBM [16-18] study showed that the inflammatory reaction is less in nano bone graft than betatricalcium phosphates graft [20,21]. Studies showed that, Nanobone is reliable and dimensionally stable bone graft [23-25].

Statins are a drug used for the treatment of hypercholestrolemia by inhibiting of 3 hydroxy 3 methylglutaryl coenzyme A reductase and convert it to mevalonate and the end results is decreasing hepatic synthesis of cholesterol [26]. Statin derivate mevalonate and suppress the expression of the receptor for activation of nuclear factor kappa B ligand and activation of nuclear factor kappa B which inhibits osteoclast differentiations and induces osteoclast apoptosis[27,28] studies showed that using of statins give rise to the so called pleiotropic effects by increasing the expression of bone morphogenetic proteins which stimulate the differentiation of osteoblast and increase its activity. Studies concluded that statin have an anabolic effect on bone [29]. Animal studies showedthat when statin applied locally give good bone regeneration [30–32] and enhance new bone formation and bone to implant contact[33].

To the best of author knowledge, the reported studies for using simvastatin to enhance the performance of osteoconductive bone substitute is limited. Therefore the aim of the presented study was to evaluate clinically and radiographically the effect of adding simvastatin to Nanobone on regenerative surgical treatment of periimplantitis during six months follow up.

PATIENTS AND METHODS

Study design

The study design was prospective, single centre, parallel randomized group and six months clinical trial. The study done to evaluate the effect of bone substitute;NanoBone (Artoss GmbH, Rostock, Germany) (group 1, control group) compared to the same bone substitute with simvastatin (Corvast 80 mg, Egyphar, Egypt) (group 2, test group) for RST of periimplantitis. 30 patients diagnosed with periimplantitis and indicated for regenerative surgical treatment for at least one periimplant bone defect selected (the most severe) and only one implant per the patient evaluated.

Periimplantitis diagnosed according to the criteria reported by the 8th European workshop on periodontology [34], at lease 2 mm or more marginal bone loss is present based on the baseline periapical x ray after the delivery of final restoration and bleeding on probing and suppuration with or without increasing of the periimplant pocket depth.

Inclusion criteria

Patient age > 18 years, have bone defect >3 mm to at least one implant, periimplant pocket depth > 5 mm with bleeding on probing and suppuration and more than 2 mm keratinized attached mucosa present. The implant system is Impla (Scheutz dental group, Germany).

Exclusion criteria

History of serious systemic disease, implants which augmented with bone graft, implant previously treated from periimplantitis and mobile implant.

Surgical procedure

Before surgical treatment, nonsurgical treatment was done to all patients by full mouth mechanical debridement and oral hygiene instructions then clinical reexamination performed one months, patient plaque score and bleeding score must below 20%.

Local anaesthesia administrated then full thickness mucoperiosteal flap done by sulcular incision around the neck of the implants (Impla implant system, Scheutz dental group) and exposed distally and mesially to expose labial and lingual/ palatal aspects of implant. Debridement of bone defect on the surfaces of implant using titanium curettes. For group I, bone defect filled with Nanobone and for group II bone defect filled with Nanobone and simvastatin. Simvastatin tablet crushed and mixed with normal saline. The flaps repositioned and sutured. All surgical procedures performed by one experienced periodontist.

Antibiotics (Augmentin 1gram 1X2) and Metronidazol (Amrizol 500 1X3) prescribed to

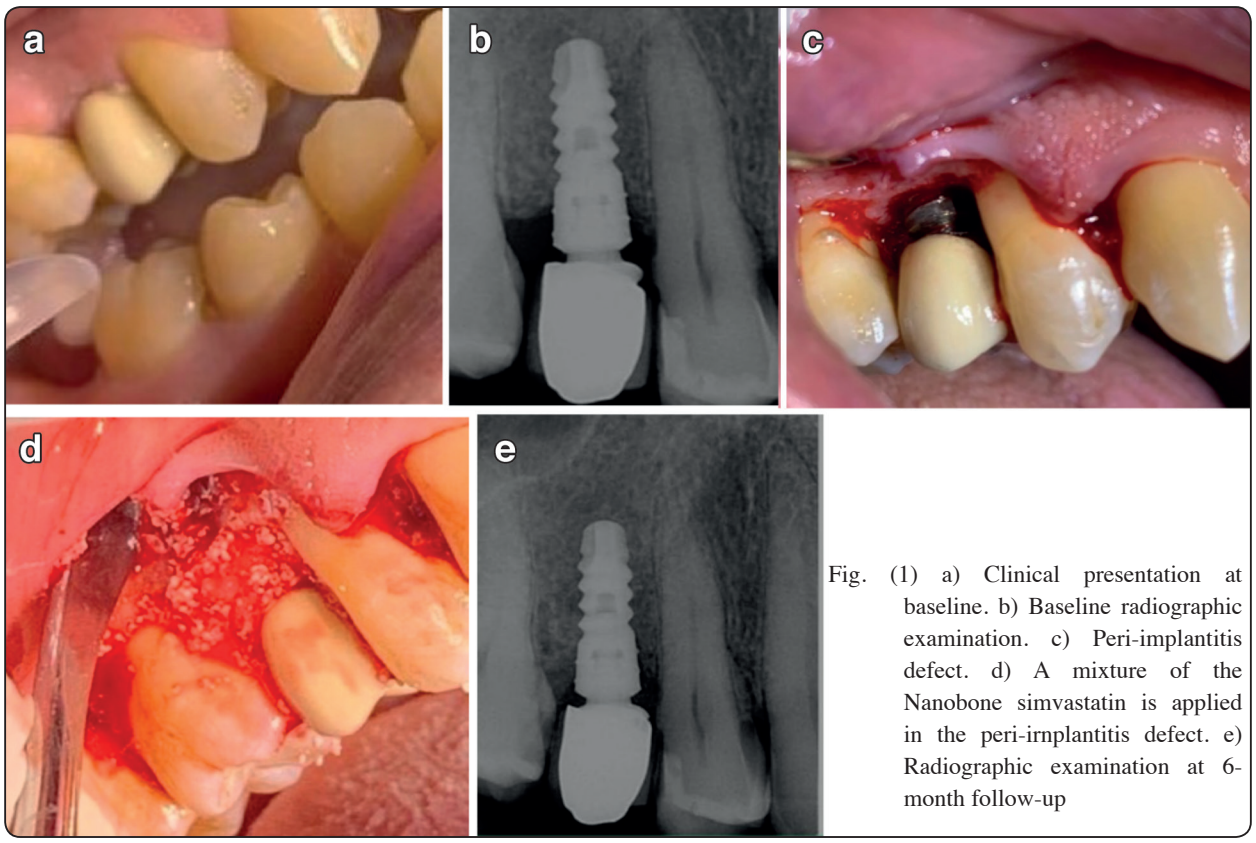

Fig. (1) a) Clinical presentation at baseline. b) Baseline radiographic examination. c) Peri-implantitis defect. d) A mixture of the Nanobone simvastatin is applied in the peri-irnplantitis defect. e) Radiographic examination at 6-month follow-up

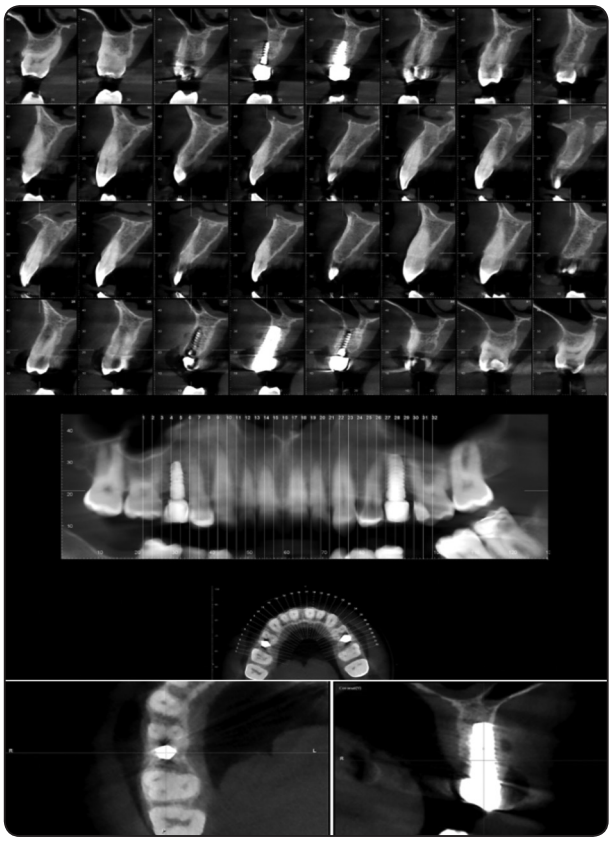

Fig. (2): Photo showing preoperative CBCT.

the patients for seven days, starting one day before the operation. Analgesic (Ibuprofen 400 mg 1X2) prescribed for three days and 0.12% chlorhexidine digluconate mouthwash twice daily for two weeks. Instruction for the patient to not brush the surgical sites for two weeks and sutures removed two weeks after surgery. At a time interval of 1, 3, and 6 months supragingival mechanical debridement has been done and reinforcement of oral hygiene measurements to the patients.

Clinical measurements

Usingm flexible plastic probe all clinical measurements recorded before and six month after the surgery. Measurements recorded at six aspects per implant. Single examiner who is blinded to the treatment assignment were responsible for evaluating the clinical parameters:

1. Plaque index (PI) marked from 0 to 3 using Loe and Silness plaque index [35]. Grade I: plaque found on the implant surface after scratching gently by probe tip. Grade II: Plaque seen by naked eye and Grade III: Large amount of plaque seen.
2. Bleeding on probing (BoP) recorded according to modified sulcus bleeding index (mSBI) as described by Mombelli [36]. Score 0: no bleeding, score I: isolated bleeding spots, score II: blood from confluent red line and score III: profuse blood.
3. Periimplant pocket depth recorded as the distance from the gingival margin to the base of the deepest periimplant pocket.
4. Mucosal recession measured as the distance from the mucosal margin and implant abutment interface.
5. Clinical attachment level defined as periimplant pocket depth plus mucosal recession.

Radiographic measurements

Using standardized long cone paralleling technique with individualised film holder introral periapical x ray films taken for involved implant. Marginal bone level evaluated by using computer assisted image analysis, author measure the distance from the abutment implant junction to bone level (bone implant contact point) and mean bone level calculated for each implant at baseline and six months postoperative. All radiological assessments performed by one investigator.

RESULTS

The study done in the clinic of periodontology department, faculty of dentistry, South Vally university. 30 patients diagnosed as periimplantitis completed the study (Table 1). Male to female ratio 2:1 and mean patients age 45.5. Bleeding and plaque scores for full mouth were less than 20% to all patients.

At the baseline, clinical characteristics of the implants with periimplantitis were comparable in group I and II regarding to overall plaque and bleeding scores for all patients (Table 1).

TABLE (1) Baseline data of the studied groups.

Parameters	**Group I**	**Group II**
Age [mean ± SD (years)]	47 (± 7)	43 (± 13)
Gender n (%) Female Male	 6 9	 4 11
Tooth (n) Central Incisor Lateral Incisor Canine First premolar Second premolar	 1 2 0 7 5	 0 3 1 5 6
FMBS (%)	16± 1.68	14.2 ± 2.71
FMPS (%)	15.1± 0.88	17.3 ± 1.01
Loading time	4.72 ± 1.01	5.21 ± 1.48

No significant intergroup differences were observed at baseline (Mann-whitneyUtest, p>0.05). FMBS (full mouth bleeding score), FMPS (full-mouth plaque score).

At six month after surgery: Plaque index shoed no significant change (P>0.05) to the baseline (Group I from 0.86 ± 0.58 to 0.45 ± 0.76 and Group II from 0.76 ± 0.78 to 0.77 ± 0.55). Bleeding index significantly (P<0.001) reduced from 1.98 ± 0.80 to 0.79 ± 0.73 in group I and from 1.87 ± 0.79 to 1.02 ± 0.07 in group II. Intragroup comparisons significant reduction in periimplant pocket depth and improvement in clinical attachment level were detected in both groups (P<0.001). The mean PPD at baseline was 6.20 ± 0.97 mm for group I and was 6.46 ± 1.02 mm for group II. These values significantly reduced to 2.73 ± 0.77 mm and 2.80 ± 0.75 mm at six months after surgery. No statistically significant difference was found regarding to mucosal recession (Table 2).

In both groups the periimplantitis were moderate, for group I the bone loss significantly reduced from 4.05 ± 1.04 mm before treatment to 2.57 ± 1.45 mm after treatment and for group II bone loss reduced from 3.86 ± 1.00 to 1.77 ± 0.70 mm. The difference between the two groups was statistically significant in favour for the test group (Table 2). No implant was lost.

TABLE (2) Descriptive statistics of the clinical and radiographic parameters at baseline and 6 months after treatment

Parameters		Baseline Mean ± SD	6 months Mean ± SD	P value Baseline vs 6 months
PI	**Group I**	0.86 ± 0.58	0.67 ± 0.45	*p*>0.05
	group II	0.76 ± 0.78	0.77 ± 0.55	*p*>0.05
	P value	0.214 [b]	0.848 [b]	
mSBI	**Group I**	1.98 ± 0.80	0.79 ± 0.73	<0.001 [a]
	Group II	1.87 ± 0.79	1.02 ± 0.07	<0.001 [a]
	P value	0.681 [b]	0.866 [b]	
PPD	**Group I**	6.20 ± 0.97	2.73 ± 0.77	<0.001 [a]
	Group II	6.46± 1.02	2.80 ± 0.75	<0.001 [a]
	P value	0.509 [b]	0.818 [b]	
CAL	**Group I**	6.50 ± 2.0	3.17 ± 1.01	<0.001 [a]
	Group II	6.96 ± 1.91	3.52 ± 0.87	<0.001 [a]
	P value	0.509 [b]	0.718 [b]	
MR	**Group I**	0.3 ± 1. 1	0.6 ± 1. 0	*p*>0.05
	Group II	0.5 ± 0.98	0.7 ± 0.68	*p*>0.05
	P value	0.507 [b]	0.717 [b]	
DF	**Group I**	4.05 ± 1.04	2.57 ± 1.45	0.037 [a]
	Group II	3.86 ± 1.00	1.77 ± 0.70	0.036 [a]
	P value	0.091 [b]	0.017 [b]	

PI, Plaque index; mSBI, mean sulcular bleeding index; PPD, Probing pocket depth; CAL, Clinical attachment level; MR, Mucosal recession; DF, Defect fill. p< .05 considered statistically significant., aWilcoxon Signed Rank Test, , bMann–Whitney U test.

DISCUSSION

Non augmentative surgical modalities for treating periimplantitis reduce the inflammation amount in short term but in long term have limited effect. For complete regeneration of periimplantitis the regenerative tissue must have sufficient strength to sustain the mechanical forces and architectural properties, porous internal structure and a surface optimised for attachment, migration, proliferation and cell differentiation [37].

This study reported on six months outcome for randomised controlled clinical trial on the surgical treatment of periimplantitis by regenerative surgical protocol utilising Nanobone graft with or without simvastatin. Study results showed that, the two treatment approaches have comparable short term results but combining simvastatin with Nanobone graft has a more positive impact on increasing the bone gain when compared with Nanobone alone. The proposed strict inclusion criteria, make all patient in the two groups homogeneous. 2 mm of keratinized attached gingiva should be present and no restorative problems diagnosed related to the implant. Studies showed that, the lack of an adequate keratinized attached gingiva is related to higher risk of periimplant inflammation and led to soft and hard tissue loss [38].

In order to include a group of patients that was as homogeneous as possible, strict inclusion criteria were proposed. This study targeted patients diagnosed with moderate to severe periimplantitis (bone defect ≥3 mm), this because it is difficult for complete resolving the periimplantitis in these patients with only non surgical debridement. In order to avoid the influence of host related factors, only one implant included even more implants were affected in the patient. The study of ***Persson et al 2001*** concluded that the quality of titanium surface is decisive importance for both osseointegration and reosseointegration, so all included implants are of the same brand (Impla implant system, scheutz dental group) [38].

Proper implant instrumentation includes removing microbial deposits without altering the implant surfaces or adversely affecting biocompatibility. Implant surface scratches may affect the titanium oxide layer, reducing the corrosion resistant nature of a titanium implant. Implant surface become contaminated with trace elements from the scaler material that remains, which compromise the long term osseointegration of the implant. ***S***tudy showed that, plastic and titanium scalers are all within safe limits for instrumenting on implant surface [39], soin this study flexible plastic probe has been used for clinical measurementsof periimplant pocket depth and titanium scaler has been used for mechanical debridement of bone defect on the surfaces of implant.

Autologous bone has osteogenic, osteoinductive and osteoconductive properties, so considered the gold stander for regeneration and bone augmentation in oral and maxillofacial surgery, but its availability is limited and restricting factors must considered due to the need for second surgical site and donor site morbidity [40].

Nanobone is fully synthetic bone graft, composed of nanohydroxyappatiete and a matrix of silica gel[41]. Nanobone is osteoconductive so it stabilize the blood clot, guide osteogenic cells to augmentation site and provide the surface for forming new bone [42]. Studies showed that, local delivery of the bioactive substances in a combination with osteoconductive bone graft could improve the treatment outcomes of periimplantitis. Statins have dual anabolic and antiresorptive effects on the bone, so considered an ideal antiosteoporotic drugs [42]. Local application of statins as adjuncts to SRP for periodontitis treatment recommended by recent systemic reviews and met-analysis based on low cost, lesser adverse effect on bacterial resistance [44]. Assessment of periimplant health is based on the clinical parameters (BoP & PPD) and marginal periimplant bone level [45]. The presented study

demonstrated high improvements regarding to PPD, BoP and CAL values at six months follow yp compared to the baseline in the two Groups. Study results showed that: the mean PPD reduction were relatively higher than the studies which used bone graft alone without biologically active materials [46-47], reported statically significant comparable improvement in the terms of the mean CAL for the two groups ($p = 0.001$) and didn't report intragroup or intergroup differences in the mean MR.

Despite the usefulness of CBCT in the detection of periimplant bone defect, beam hardening artefacts from dental implant may affect its diagnostic performance. The higher resolution with 10 to 25 line pairs per mm (lp/mm) for intraoral radiographs facilitates a higher accuracy in displaying details, while CBCT reveal a lower resolution with only 1 to 2 lp/mm, and has a smaller distortion and magnification effects [48]**.** Studies reported that CBCT was less accurate for assessing periimplant bone loss than intraoral radiographs [49]. Results showed limitations of CBCT in accurately determining the bone levels of implants in the vertical as well as the horizontal dimensions [50]. This conducted with the preoperative radiological evaluation (CBCT and periapical x ray) for all patients in this study **(Fig. 2).** Stefane R et al. 2019 recommended long cone paralleling introral periapical x ray films to assess interproximal crestal bone changes around the implants [51].So in this study standardized long cone paralleling technique with individualised film holder introral periapical x ray films has been used for the evaluation of the involved implant.

The results of this study showed that, the mean radiographic amount of bone fill in the test group was about 2.09 ± 0.79 mm, this mean defect bone fill of approximately 54%, which higher than that observed in the control group in which the defect bone fill was 1.48 ± 1.05 (about 36.5%), this beneficial effects of simvastatin attributed to their immunoregurato-ry effects on epithelial cells in addition to its dual anabolic and antiresorptive effects [47], as well as it has antibacterial properties [48]. Clinical studies showed that simvastatin has pleiotropic effects on periodontitis patients, they expressed lower IL-1 levels on statin medication [49], down-regulation of IL-1β, myeloperoxidase levels, and higher anti-inflammatory IL-10 levels in gingival crevicular fluid compared to patients without statin treatment [50].

In conclusion, this study suggested that, adjunctive use of simvastatin with Nanobone seems to br beneficial for regenerative surgical treatment of periimplantitis.

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