Original Article

A Clinical and Radiographic Evaluation of the Efficacy of Nanohydroxyapatite (Sybograf™) versus Bioactive Calcium Phosphosilicate Putty (Novabone®) in the Treatment of Human Periodontal Infrabony Defects: A Randomized Clinical Trial

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Abstract

Aim: The aim of this study is to compare and to evaluate clinically and radiographically the bone regeneration and the amount of bone fill (BL) between nanocrystalline hydroxyapatite (Nc-HA) (Sybograf™) and bioactive synthetic NovaBone Putty in the treatment of intrabony component of periodontal osseous defects. **Materials and Methods:** Twenty sites in 20 patients, within the age range of 25–55 years, showing intrabony defects were selected and divided into Group I (Nc-HA) and Group II (Bioactive synthetic NovaBone Putty). All the selected sites were assessed with the clinical and radiographic parameters such as plaque index, gingival index, sulcus bleeding index, probing pocket depth, clinical attachment level, gingival recession, and radiographic BL. All the clinical and radiographic parameter values obtained at different intervals (baseline, 3, and 6 and 9 months) were subjected to statistical analysis. **Results:** A statistically significant reduction in pocket depth of 4.400 ± 0.843 mm (Group I), 3.800 ± 0.789 mm (Group II) and gain in clinical attachment level of 6.2 mm (Group I), 5.9 mm (Group II) were recorded at the end of the study. A slight increase in gingival recession was observed. The mean percentage changes in the amount of radiographic BL of Group II and Group I were significant, However, when compared between the groups, there is no significant difference in BL observed. **Conclusion:** Both the graft materials appear to have nearly comparable effects, with nanocrystalline hydroxyapatite (Sybograf™), displaying slightly superior effect over bioactive glass especially in relation to clinical parameters. However, long-term, controlled clinical trials are required to confirm these findings.

Keywords: *NovaBone Putty, periodontal osseous defects, probing pocket depth, radiographic bone fill, Sybograf™*

Introduction

Periodontal disease is the inflammation of supporting tissues of teeth, leading to progressive attachment loss and bone loss around the teeth leading to the pocket formation and/or recession.[1] The goal of any periodontal therapy is to regenerate the lost periodontium, a process which may include regeneration of multiple tissues including cementum, periodontal ligament, and bone. One of the best approaches to achieve this regeneration is the use of bone graft materials, which includes autografts, xenografts, and alloplastic materials.[2]

Various alloplastic materials that are available today in the market are synthetic substances that are used to fill bone defects. The bioactive glasses are one such materials that have been used extensively in medicine for middle ear surgery[3] and have been applied to dentistry in the treatment of bone defects, ridge preservation, and periodontal bone defects.[4] Bioactive glass is a biocompatible product, that has reported to exert a positive influence on osteoblast culture and inhibitory capacity on fibroblast proliferation and on the apical migration of the junctional epithelium.

NovaBone® Putty is a bioactive material which is a composite of synthetic, absorbable binder and bioactive calcium-phospho-silicate particulate which shows both osteostimulatory and osteoconductive properties.However, the stimulatory action has been demonstrated, to be more rapid than simple osteoconduction

How to cite this article: Koduru S, Aghanashini S, Nadiger S, Apoorva SM, Bhat D, Puvvalla B. A clinical and radiographic evaluation of the efficacy of nanohydroxyapatite (Sybograf™) versus bioactive calcium phosphosilicate putty (Novabone®) in the treatment of human periodontal infrabony defects: A randomized clinical trial. Contemp Clin Dent 2019;10:16-23.

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Access this article online

Website: www.contempclindent.org

DOI: 10.4103/ccd.ccd_52_18

Quick Response Code:

in various *in vitro* studies.[5,6] Recently, an another synthetic nanocrystalline hydroxyapatite (Nc-HA) paste containing about 65% water and 35% nanostructured apatite particles, has been introduced for augmentation procedures in osseous defect. Advantages of Nc-HA material are osteoconductivity, bioresorbability, and close contact.[7]

Studies were conducted comparing the repair response of placement of NovaBone Putty after open flap debridement (OFD) and OFD alone, comparing the efficacy of NovaBone Putty with NovaBone particulate, evaluating the efficacy of Nc-HA with autogenous bone graft, collagen membrane individually but literature lacks studies comparing the effects of Nc-HA and NovaBone Putty. Hence, an attempt is made in the present study to compare and evaluate, clinically and radiographically, the efficacy of NovaBone® Putty and Nc-HA (Sybograf™) in the treatment of periodontal endosseous defects.

Materials and Methods

Study population and design

A randomized clinical study was carried out in the Department of Periodontology, D. A. P. M. R. V. Dental College, Bengaluru. The study was carried out in 20 defects present in 20 patients aged between 25 and 55 years. The participants were explained about the study, and a written consent was obtained from each of the participants.

Participants were selected from those diagnosed as having chronic periodontitis (based on the AAP World Workshop 1999 classification of periodontal diseases and conditions), with interproximal probing depth ≥5 mm following Phase I therapy and radiographic evidence of angular bone loss and indicated for regenerative periodontal surgery.

The patients were randomly divided into two groups and were followed up for a period of 9 months.

The groups were as follows:
- Group I (n = 10 defects) - those to be treated with synthetic bone graft particles Nc-HA (Sybograf™)
- Group II (n = 10 defects) - those to be treated with bioactive glass synthetic bone graft (NovaBone® Putty).

The participants were included in the study based on the following inclusion and exclusion criteria.

Inclusion criteria

- No systemic conditions that would contraindicate routine periodontal procedures
- Interproximal probing depth ≥5 mm following Phase I therapy
- The sites having radiographic evidence of angular bone loss ≥3 mm deep.

Exclusion criteria

- Participants who had received periodontal flap/regenerative therapy within the past 1 year
- Pregnant and lactating patients
- Smokers
- Patients who were on antibiotic and nonsteroidal anti-inflammatory drugs within the past 1 year.

The patients were subjected to plaque index (PI), gingival index, probing pocket depth (PPD), relative attachment level (RAL), and gingival recession (GR). All clinical parameters were recorded preoperatively at baseline, and postoperatively, after 3, 6, and 9 months. PPD and RAL were recorded to the nearest millimeter by a single examiner using a University of North Carolina-15 probe.

Intraoral periapical radiographs were taken for all selected sites, using digital radiographic technique preoperatively and postoperatively. The vertical dimension between the projection of the bone crest on the root surface bone crest projection (BCP) and the most coronal level along the root surface where the periodontal ligament space was considered to have a normal width bottom of the bone defect (BoBD) was measured as BCP-BoBD which gives the depth of the intrabony. Before the surgical treatment, patients received initial periodontal therapy with oral hygiene prophylaxis, professional tooth cleaning, and scaling.

Surgical protocol

After the presurgical evaluation and satisfactory response to Phase I therapy, patients were subjected to surgical protocol under aseptic conditions. Routine preparation with povidone-iodine was carried out and local anesthesia (2% lignocaine hydrochloride with 1 in 80,000 adrenaline) was instituted. Then, crevicular incisions were given using No. 15 blade and the flaps were elevated using blunt dissection with the help of a No. 9 molt periosteal elevator. The lining pocket epithelium was removed so that a fresh connective tissue bed was in contact with the graft material and utmost care was taken to preserve the interdental papilla. This was done to allow better coverage of the graft material interproximally and prevent exposure and exfoliation of the graft as well as to aid in better healing. A thorough debridement was carried out using curettes #7–8, # 9–10, #11–12, and #13–14 in all the defect areas. All the granulation tissue was removed to ensure a clean site followed by thorough root planing. Before the placement of the graft, a 3-0 nonresorbable braided silk suture was passed through the buccal and lingual papillae, and the suture was left loose. This was done to prevent removal of the graft particles by the passage of the needle as well as the suture material. An adequate quantity of synthetic Nc-HA graft (Sybograf™) was mixed with a few drops of saline in a sterile dappen dish.

The graft placement site was selected randomly. Group I patients received synthetic bone graft particles

Nc-HA (Sybograf™) [Figure 1] and Group II patients received synthetic bioactive graft material (Novabone® Putty) [Figure 2]. The suturing was then completed and noneugenol periodontal dressing (Coe Pack™, GC America Inc., Chicago, IL, USA) was placed.

All patients were prescribed with systemic-amoxicillin 500 mg three times per day for 5 days and an analgesic-a combination of acetaminophen 500 mg; diclofenac sodium 50 mg twice daily per day for 3 days). Patients were instructed to rinse with chlorhexidine digluconate (0.2%) mouthwash twice daily for 2 weeks, and the patients were discharged with postoperative instructions.

Statistical analysis

The arithmetic mean and standard deviations were calculated for the requisite assessment intervals. Student's *t*-test was used for statistical analysis.

Results

A total number of 20 patients in the age group of 25–55 years with radiographic evidence of intrabony defects were selected for the study. Clinical evaluation of postsurgical healing revealed a good soft-tissue response to the graft materials with no adverse complications.

Intra-group comparison: Group I [Figure 3 and Graph 1]

At the end of 9 months, statistically significant reduction of probing depth from 8.900 ± 2.424–4.400 ± 0.843 was observed [Table 1]. In addition, at the end of 9 months, statistically significant change in RAL from 10.400 ± 1.430 to 4.200 ± 0.632 with attachment level gain of approximately 6.2 mm was observed [Table 2]. While, the extent of GR was increasing from 1.500 ± 1.080 at baseline to 2.100 ± 0.738 at 3 months, 1.800 ± 0.919 at 6 months, and observed to be reduced to 1.700 ± 0.949 at the end of 9 months [Table 3].

Intra-group comparison: Group II [Figure 4]

At the end of 9 months, statistically significant reduction of probing depth from 8.900 ± 2.424 to 3.800 ± 0.789 was observed [Table 1]. In addition, at the end of 9 months, statistically significant change in RAL from 10.200 ± 1.506 to 4.300 ± 0.483 with attachment level gain of approximately 5.9 mm was observed [Table 2]. The GR from 1.700 ± 1.059 at baseline increased to 2.100 ± 0.876 at 3 months, 1.800 ± 0.919 at 6 months and reduced to 1.700 ± 0.949 at the end of 9 months [Table 3].

Intergroup comparison

The mean difference in the values of PPD between two groups at baseline, 3 months, 6 months and 9 months were 0.000, 0.200, 0.500, and 0.600, respectively. No significant difference was observed between the two groups at any of the time intervals with respect to mean PPD ($P > 0.05$) [Table 4 and Graph 2].

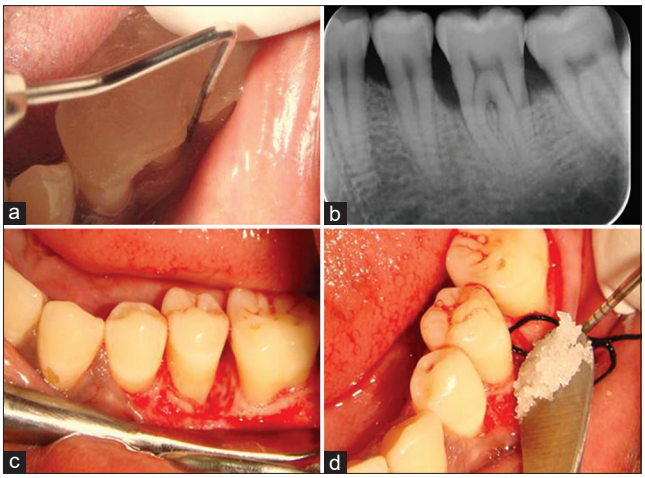


Figure 1: Group I (a) preoperative probing pocket depth (b) radiograph of defect (c) debridement of the defect area (d) placement of nanocrystalline hydroxyapatite (Sybograf™)

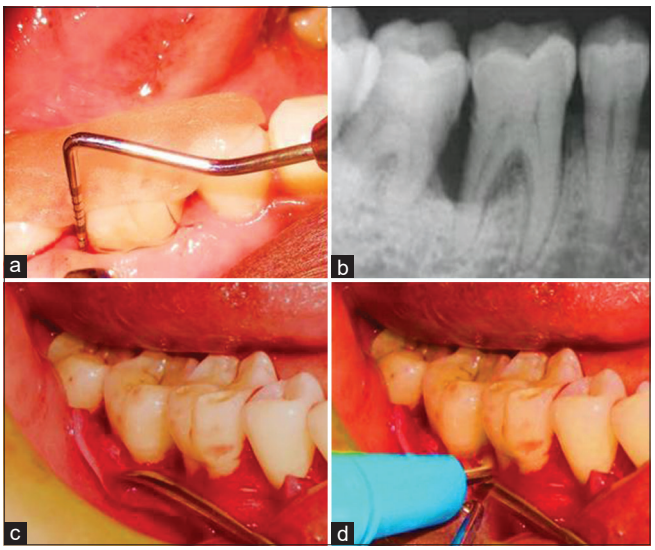


Figure 2: Group II (a) preoperative probing pocket depth (b) radiograph of defect (c) debridement of the defect area (d) placement of bioactive glass synthetic bone graft (NovaBone® Putty)

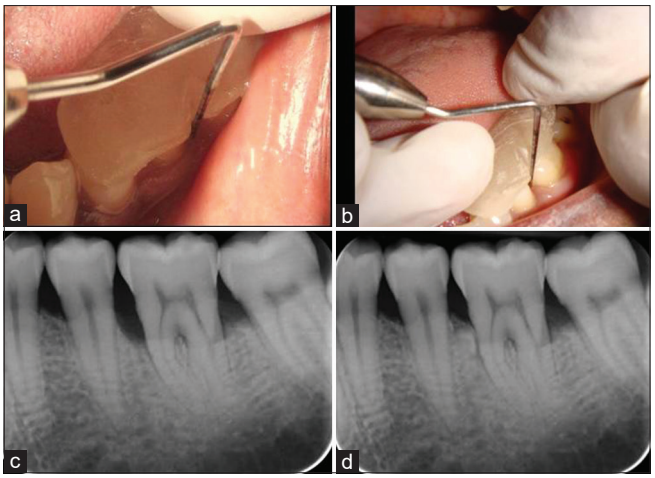


Figure 3: Group I (a and b) Significant reduction probing pocket depth after 9 months of surgery (c and d) significant fill of defect after 9 months of surgery

The mean difference in the values of RAL between two groups at baseline, 3 months, 6 months, and 9 months were −0.200, 0.100, 0.100, and −0.100, respectively. No significant difference was observed between the two groups at any of the time intervals with respect to mean RAL ($P > 0.05$) [Table 4].

The mean difference in the values of GR between two groups at baseline, 3 months, 6 months, and 9 months were −0.200, 0.000, 0.000, and 0.000, respectively. No significant difference was observed between the two groups at any of the time intervals with respect to mean GR ($P > 0.05$) [Table 5].

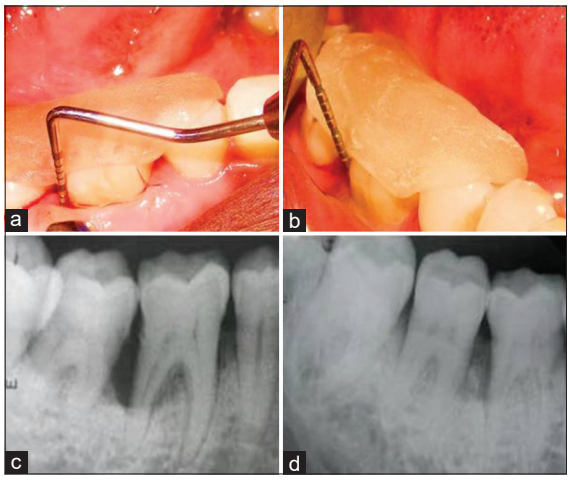


Figure 4: Group II (a and b) significant reduction probing pocket depth after 9 months of surgery (c and d) significant fill of defect after 9 months of surgery

Radiographic parameters

Analysis of the radiological parameters revealed significant mean percentage change in the amount of radiographic fill in Group I and Group II [Table 6 and Graph 3]. The intergroup differences were statistically insignificant, which indicate percentage change in radiographic bone fill (BL) was equal in both the groups [Table 7 and Graph 4].

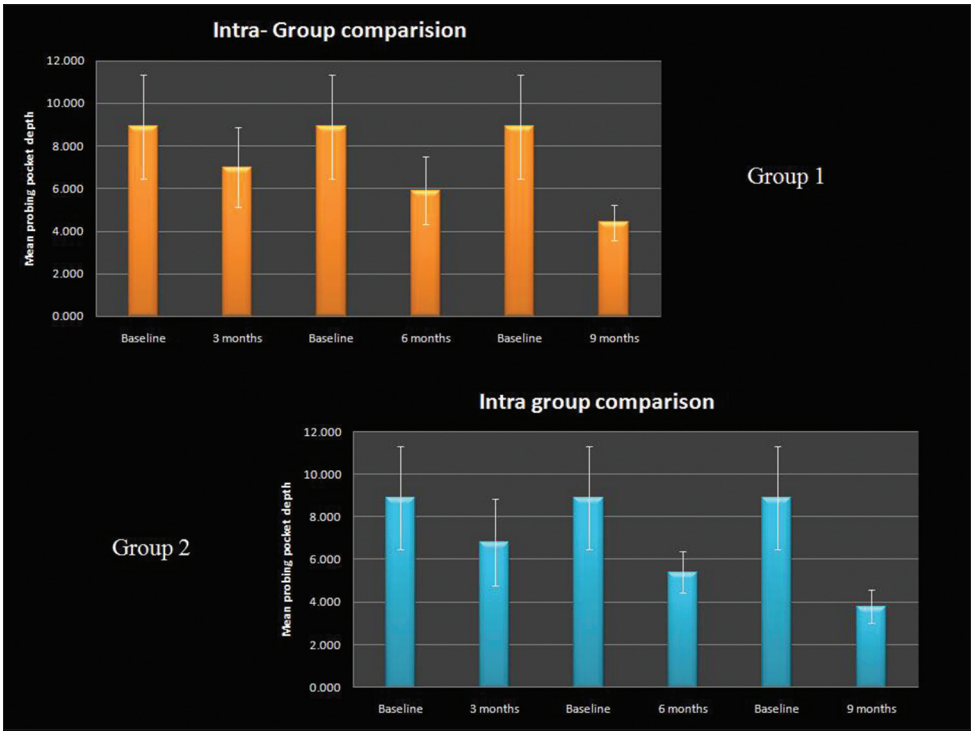
Discussion

NovaBone Putty (manufactured by NovaBone, Florida) is a bioactive synthetic graft material that shows both osteostimulative and osteoconductive properties. It is available in putty consistency and has two particle phases. Its putty consistency makes it easy to manipulate and adapts well to defects, while the particle phases enhance the physical characteristics and improve handling properties, also, spaces between particles

Table 1: Probing pocket depth - Intra-group comparison

GROUP - I			GROUP-II			*P*
Time interval	Mean	Standard deviations	Time interval	Mean	Standard deviations	
Baseline	8.900	2.424	Baseline	8.900	2.424	<0.01*
3 months	7.000	1.886	3 months	6.800	2.044	
Baseline	8.900	2.424	Baseline	8.900	2.424	<0.01*
6 months	5.900	1.595	6 months	5.400	0.966	
Baseline	8.900	2.424	Baseline	8.900	2.424	<0.01*
9 months	4.400	0.843	9 months	3.800	0.789	

*Denotes significant difference



Graph 1: Probing pocket depth – intragroup comparison

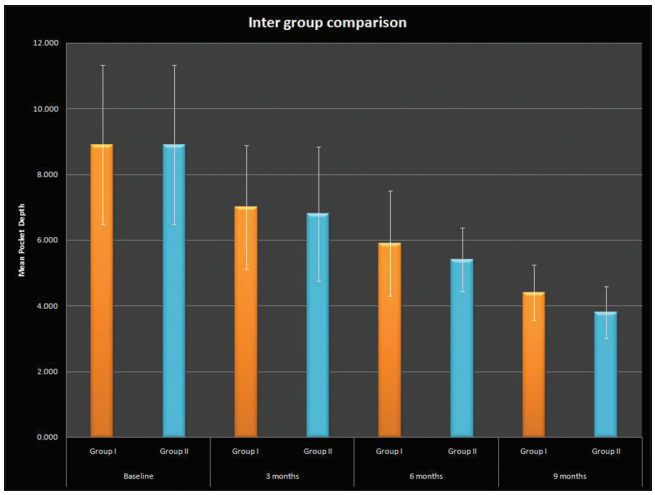
permit rapid vascularization and bone ingrowth. Because of the above properties, bone formation occurs in several areas in the defect simultaneously, thus enhancing the regeneration.[8]

Hydroxyapatite is a bioactive ceramic alloplastic material that shows a uniform pore size, which facilitates the ingrowth of vascular channels and subsequent formation of new bone.[9] Controlled studies in humans show that it produces more BL in intrabony lesions than surgical debridement alone.[10] Kenney *et al*. showed histological evidence of new bone formation on the surface of and within the pores of porous hydroxyapatite. Light and scanning electron microscopical examination showed spreading osteoblasts and new bone in contact with the particles.[11]

We have chosen nanocrystaline hydroxyapatite in this study since nanomaterials have significant surface effects, size effects, quantum effects, and exhibit much better performance properties than traditional materials. Another important feature of these nanostructured materials is the development of self-assembly.[12]

In the present study, patients with probing depth >5 mm were included since it was reported that the surgical procedures would induce loss of attachment if done in pockets shallower than 4.2 mm, according to a study done by Lindhe *et al*.[13]

The results of the present study showed a statistically significant decrease in the PI from baseline to 3 months, 6 months, and 9 months in Group I as well as in Group II

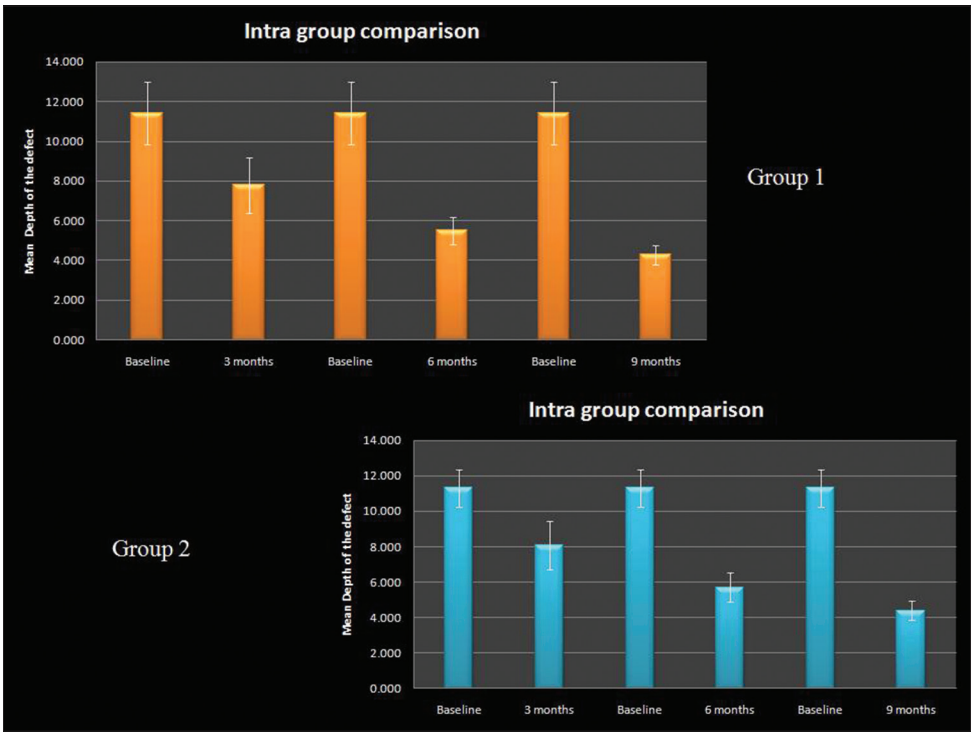


Graph 2: Probing pocket depth – intergroup comparison

Table 2: Relative attachment level- Intra-group comparison

GROUP - I			GROUP - II			*P*
Time interval	**Mean**	**Standard deviations**	**Time interval**	**Mean**	**Standard deviations**	
Baseline	10.400	1.430	Baseline	10.600	1.506	<0.01*
3 months	8.000	1.491	3 months	7.900	1.449	
Baseline	10.400	1.430	Baseline	10.600	1.506	<0.01*
6 months	5.700	0.949	6 months	5.600	0.966	
Baseline	10.400	1.430	Baseline	10.600	1.506	<0.01*
9 months	4.200	0.632	9 months	4.300	0.483	

*Denotes significant difference



Graph 3: Depth of the defect – intragroup comparison

Table 3:Gingival recession- Intra-group comparison

GROUP -I				GROUP-II			
Time Interval	Mean	Standard deviations	*P*	Time Interval	Mean	Standard deviations	*P*
Baseline	1.500	1.080	0.005*	Baseline	8.900	2.424	0.037*
3 months	2.100	0.738		3 months	6.800	2.044	
Baseline	1.500	1.080	0.394	Baseline	8.900	2.424	0.758
6 months	1.800	0.919		6 months	5.400	0.966	
Baseline	1.500	1.080	0.591	Baseline	8.900	2.424	1.000
9 months	1.700	0.949		9 months	3.800	0.789	

*Denotes significant difference

Table 4:Inter- group comparison

	Time	Group	Mean	Standard deviations	*P*
PPD	Baseline	Group I	5.933	2.424	.i
		Group II	8.900	2.424	
	3 months	Group I	7.000	1.336	0.823
		Group II	6.800	2.044	
	6 months	Group I	5.900	1.595	0.408
		Group II	5.400	0.966	
	9 months	Group I	4.400	0.843	0.118
		Group II	3.300	0.789	
	Time	**Group**	**Mean**	**Standard deviations**	***P***
RAL	Baseline	Group I	10.400	1.430	0.764
		Group II	10.600	1.506	
	3 months	Group I	3.000	1.491	0.881
		Group II	7.900	1.449	
	6 months	Group I	5.700	0.949	S. 813
		Group II	5.600	0.966	
	9 months	Group I	4.200	0.632	C, 5Q5

Table 5: Inter- group comparison

	Time	Group	Mean	Standard deviations	*P*
Gingival recession	Baseline	Group I	1.500	1.030	0.661
		Group II	1.700	1.059	
	3 months	Group I	2.100	0.738	1.000
		Group II	2.100	0.376	
	6 months	Group I	1.300	0.919	1.000
		Group II	1.300	0.919	
	9 months	Group I	1.700	0.949	1.000
		Group II	1.700	0.949	
		Group II	4.400	0.516	

Table 6: Depth of the defect - Intra-group comparison

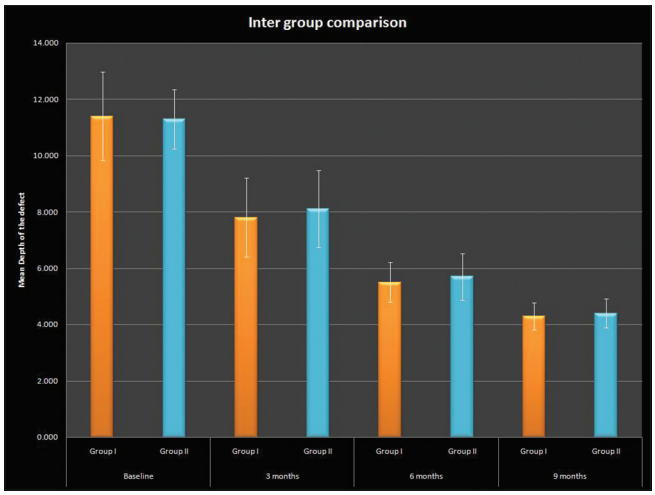
GROUP - I			GROUP-II			*P*
Time Interval	Mean	Standard deviations	Time Interval	Mean	Standard deviations	
Baseline	11.400	1.578	Baseline	11.300	1.059	<0.01*
3 months	7.800	1.398	3 months	8.100	1.370	
Baseline	11.400	1.578	Baseline	11.300	1.059	<0.01*
6 months	5.500	0.707	6 months	5.700	0.823	
Baseline	11.400	1.578	Baseline	11.300	1.059	<0.01*
9 months	4.300	0.483	9 months	4.400	0.516	

which was in accordance with the study done by Döri *et al*. who compared the effect of platelet rich plasma with on the healing of infrabony defects treated with natural bone mineral with guided-tissue regeneration (GTR) membrane and anorganic bovine bone mineral with GTR membrane.[14,15] However, no statistically significant difference was observed between the two groups at any of the time intervals suggesting that there was a good maintenance of oral hygiene throughout the study in both the groups and all patients were very well motivated for obtaining a successful treatment outcome.

PPD reduced from 8.900 ± 2.424 to 4.400 ± 0.843 in Group I and from 8.900 ± 2.424 to 3.800 ± 0.789 in Group II at the end of 9 months. The difference was found to be statistically significant between the groups. These reductions in the PPD can be attributed to soft- and hard-tissue improvements following the resolution of inflammation and to the osteogenic potential of bone graft materials used in the study. The findings of the study seen in Group I were in concordance with studies conducted by Kenney *et al*.[16] Kasaj *et al*.,[17] and Horváth *et al*.[18] The results of the study seen in Group II are in agreement to the previous studies of Froum *et al*.,[19] Lovelace *et al*., and[20] Mengel *et al*. However, no statistically significant difference was observed between the two groups at any of the time intervals suggesting that both the treatment options are equally efficient in reduction of PPD.

The results of RAL in the present study showed that the attachment level gain of approximately 6.2 mm and 5.9 mm in Group I and Group II, respectively, at the end of 9 months which was statistically significant. The results of Group I were similar with the previous studies conducted by Stahl *et al*.,[21] Rohit jain *et al*.,[22] and the results in Group II were in accordance with the studies done by Anderegg *et al*.[23] Froum *et al*.,[19] Subbaiah and Thomas.[4] This gain in attachment level can be attributed to periodontal regeneration, long junctional epithelium formation and/or soft-tissue healing at the base of the pocket.

The GR in Group I have increased from 1.500 ± 1.080 at baseline to 1.700 ± 0.949 at the end of 9 months. An increase in GR seen in Group I may be attributed to



Graph 4: Depth of the defect – intergroup comparison

Table 7: Inter- group comparison

	Time	Group	Mean	Std Dec	*P*
Depth of defect	Baseline	Group I	11.400	1.573	0.370
		Group II	11.300	1.059	
	3 months	Group I	7.300	1.393	0.634
		Group II	3.100	1.370	
	6 months	Group I	5.500	0.707	0.567
		Group II	5.700	0.323	
	9 months	Group I	4300	0.433	0.660
		Group II	4.400	0.516	

the shrinkage of gingival tissues with the resolution of inflammation. These findings are in consistency with Froum *et al*.,[19] Mengel *et al*.,[24] Sculean *et al*.[25] who reported an increase of 1.29, 1.20, 1.28, mm in GR, respectively, after 6 months of implantation of graft material.

There was a BL of about 7.00 ± 0.543 mm and 7.10 ± 1.095 mm in Group I and II, respectively, at the end of 9 months. The results of Group I are in accordance with studies done by Mengel *et al*.,[24] Froum *et al*.,[19] and Lovelace *et al*.[20] who showed a mean BL of 65.0%, 62.0%, and 61.8%, respectively in the bioactive glass treated sites. The results of Group II are in accordance with studies done by Yukna *et al*.,[26] Kasaj *et al*.[17] However, the amount of BL between the groups was statistically insignificant, which indicate percentage change in radiographic BL was equal in both the groups.

We also found no antigenic or inadvertent reactions or tissue responses during the course of the study, indicating the safety of these bone grafts as clinical materials.

Conclusion

Within the limitations of the study, the results indicate that both Nc-HA and bioactive glass synthetic bone graft particles are efficacious in the treatment of periodontal endosseous defects. Both the graft materials appear to have nearly comparable effects, with Nc-HA (Sybograf™), displaying slightly superior effect over bioactive glass was observed especially in relation to clinical parameters. However, long-term, multicenter randomized, controlled clinical trials will be required to discern the definite clinical and radiographic effects of these graft materials and to arrive at an explicit conclusion.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Prathap S, Hegde S, Kashyap R, Prathap MS, Arunkumar MS. Clinical evaluation of porous hydroxyapatite bone graft (Periobone G) with and without collagen membrane (Periocol) in the treatment of bilateral grade II furcation defects in mandibular first permanent molars. J Indian Soc Periodontol 2013;17:228-34.
2. Kasaj A, Willershausen B, Reichert C, Röhrig B, Smeets R, Schmidt M, *et al.* Ability of nanocrystalline hydroxyapatite paste to promote human periodontal ligament cell proliferation. J Oral Sci 2008;50:279-85.
3. Reck R, Störkel S, Meyer A. Bioactive glass-ceramics in middle ear surgery. An 8-year review. Ann N Y Acad Sci 1988;523:100-6.
4. Subbaiah R, Thomas B. Efficacy of a bioactive alloplast, in the treatment of human periodontal osseous defects-a clinical study. Med Oral Patol Oral Cir Bucal 2011;16:e239-44.
5. Oonishi H, Kushitani S, Yasukawa E, Iwaki H, Hench LL, Wilson J, *et al.* Particulate bioglass compared with hydroxyapatite as a bone graft substitute. Clin Orthop Relat Res 1997;334:316-25.
6. Fujishiro Y, Hench LL, Oonishi H. Quantitative rates of *in vivo* bone generation for bioglass and hydroxyapatite particles as bone graft substitute. J Mater Sci Mater Med 1997;8:649-52.
7. Singh VP, Nayak DG, Uppoor AS, Shah D. Nano-crystalline hydroxyapatite bone graft combined with bioresorbable collagen membrane in the treatment of periodontal intrabony defects: A randomized controlled clinical trial. J Indian Soc Periodontol 2012;16:562-8.
8. Bembi NN, Bembi S, Mago J, Baweja GK, Baweja PS. Comparative evaluation of bioactive synthetic NovaBone putty and calcified algae-derived porous hydroxyapatite bone grafts for the treatment of intrabony defects. Int J Clin Pediatr Dent 2016;9:285-90.
9. Barnett JD, Mellonig JT, Gray JL, Towle HJ. Comparison of freeze-dried bone allograft and porous hydroxylapatite in human periodontal defects. J Periodontol 1989;60:231-7.
10. Yukna RA. Osseous defect responses to hydroxylapatite grafting versus open flap debridement. J Clin Periodontol 1989;16:398-402.
11. Kenney EB, Lekovic V, Sa Ferreira JC, Han T, Dimitrijevic B, Carranza FA Jr., *et al.* Bone formation within porous hydroxylapatite implants in human periodontal defects. J Periodontol 1986;57:76-83.
12. Kong LX, Peng Z, Li SD, Bartold PM. Nanotechnology and its role in the management of periodontal diseases. Periodontol 2000 2006;40:184-96.

13. Lindhe J, Socransky SS, Nyman S, Haffajee A, Westfelt E. "Critical probing depths" in periodontal therapy. J Clin Periodontol 1982;9:323-36.
14. Döri F, Huszár T, Nikolidakis D, Arweiler NB, Gera I, Sculean A, *et al.* Effect of platelet-rich plasma on the healing of intra-bony defects treated with a natural bone mineral and a collagen membrane. J Clin Periodontol 2007;34:254-61.
15. Döri F, Huszár T, Nikolidakis D, Arweiler NB, Gera I, Sculean A, *et al.* Effect of platelet-rich plasma on the healing of intrabony defects treated with an Anorganic bovine bone mineral and expanded polytetrafluoroethylene membranes. J Periodontol 2007;78:983-90.
16. Kenney EB, Lekovic V, Han T, Carranza FA Jr., Dimitrijevic B. The use of a porous hydroxylapatite implant in periodontal defects. I. Clinical results after six months. J Periodontol 1985;56:82-8.
17. Kasaj A, Röhrig B, Zafiropoulos GG, Willershausen B. Clinical evaluation of nanocrystalline hydroxyapatite paste in the treatment of human periodontal bony defects – A randomized controlled clinical trial: 6-month results. J Periodontol 2008;79:394-400.
18. Horváth A, Stavropoulos A, Windisch P, Lukács L, Gera I, Sculean A, *et al.* Histological evaluation of human intrabony periodontal defects treated with an unsintered nanocrystalline hydroxyapatite paste. Clin Oral Investig 2013;17:423-30.
19. Froum SJ, Weinberg MA, Tarnow D. Comparison of bioactive glass synthetic bone graft particles and open debridement in the treatment of human periodontal defects. A clinical study. J Periodontol 1998;69:698-709.
20. Lovelace TB, Mellonig JT, Meffert RM, Jones AA, Nummikoski PV, Cochran DL, *et al.* Clinical evaluation of bioactive glass in the treatment of periodontal osseous defects in humans. J Periodontol 1998;69:1027-35.
21. Stahl SS, Froum S. Human intrabony lesion responses to debridement, porous hydroxyapatite implants and teflon barrier membranes 7 histologic case reports. J Clin Periodontol 1991;18:605-10.
22. Jain R, Kaur H, Jain S, Kapoor D, Nanda T, Jain M. Comparison of nano-sized hydroxyapatite and b-tricalcium phosphate in the treatment of human periodontal intrabony defects. J Clin Diagn Res 2014;8:74-8.
23. Anderegg CR, Alexander DC, Freidman M. A bioactive glass particulate in the treatment of molar furcation invasions. J Periodontol 1999;70:384-7.
24. Mengel R, Soffner M, Flores-de-Jacoby L. Bioabsorbable membrane and bioactive glass in the treatment of intrabony defects in patients with generalized aggressive periodontitis: Results of a 12-month clinical and radiological study. J Periodontol 2003;74:899-908.
25. Sculean A, Pietruska M, Arweiler NB, Auschill TM, Nemcovsky C. Four-year results of a prospective-controlled clinical study evaluating healing of intra-bony defects following treatment with an enamel matrix protein derivative alone or combined with a bioactive glass. J Clin Periodontol 2007;34:507-13.
26. Yukna RA, Mayer ET, Amos SM 5-year evaluation of durapatite ceramic alloplastic implants in periodontal osseous defects. J Periodontol 1989;60:544-51.