Original Article

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Dentistry Section

Efficacy of a Combination of β-Tricalcium Phosphate with Hyaluronic Acid in the Management of Intrabony Periodontal Defects: A Prospective Clinical Study

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ABSTRACT

Introduction: Numerous bioactive grafts have been studied for periodontal defect regeneration of which, β-Tricalcium Phospate (β-TCP) is a very promising bone graft. Hyaluronic Acid (HA), an essential component of periodontal ligament matrix plays a pivotal role in tissue growth, repair and remodeling.

Aim: To evaluate the efficacy of 0.8% HA as an adjunct to β-TCP in the treatment of isolated human intrabony defects.

Materials and Methods: This prospective clinical study was conducted at the Department of Periodontics, SRM Dental College, Chennai, Tamil Nadu, India, from January 2017 and December 2017 (followed-up to June 2018). The study included 30 intrabony defects from 16 chronic periodontitis patients, 15 of each were randomly assigned into either test/control groups and were reviewed till six months. After phase I therapy regenerative osseous surgery was performed at all the sites. Control sites received β-TCP bone graft alone and test group received β-TCP with 0.8% HA. Postsurgical clinical evaluation of Probing Pocket depth (PPD) and Clinical Attachment level (CAL) was done at three and six months, radiographs were repeated at six months to assess the bone fill. Statistical analysis using Statistical Package for the Social Sciences (SPSS) version 22.0 was done, Mann-Whitney U test and Wilcoxon-Signed Rank test were used to compare the intergroup and intragroup values respectively.

Results: The mean age of the control and test groups were 45.7 and 48.5 years respectively. The PPD was reduced, CAL and bone fill were increased in both groups from baseline, indicating clinical effectiveness. From baseline to six months, the PPD reduction and gain in CAL in the test and control groups were 3.27±0.18 mm, 3.20±0.18 mm and 3.07±0.03 mm, 3.07±0.08 mm, respectively, which was statistically significant (p-value <0.001). However, intergroup comparison revealed no statistical significance (p>0.05) in both clinical and radiographic parameters.

Conclusion: Hyaluronic acid as an adjunct to β-TCP demonstrated only comparable outcomes despite obtaining substantial bone fill and attachment gain.

Keywords: Bone fill, Bone grafts, Hyaluronan, Periodontitis, Regeneration

INTRODUCTION

Periodontitis is an inflammatory condition in which the alveolar bone, cementum, periodontal ligament, and gingiva are destroyed in response to insults caused by microbial accumulations on tooth surfaces [1]. The periodontium features a highly regulated expression of certain innate host defence mediators to cope with the continual microbial inflow. A rise in the concentration of these mediators is one of the consequences of periodontal disease, characterised by alveolar bone loss. The ratio of Receptor-Activator of Nuclear Factor-B Ligand (RANKL) to Osteoprotegerin (OPG) is the key regulator of normal bone resorption and deposition activities that occur during bone remodelling, and this process most likely contributes to the bone loss seen in periodontitis [2].

One of the most extensively used procedures for regaining the lost periodontal attachment apparatus is the use of bone substitutes to fill intrabony periodontal defects [3]. The basic goal of periodontal regeneration is the development of new attachment. Periodontal Regeneration is defined as the reproduction or restoration of lost or diseased tissues in order to restore the periodontium's architecture and function [3]. Various bioactive materials such as recombinant Bone Morphogenic Protein (rhBMP), Platelet Derived Growth Factor (PDGF) that are part of the natural healing process have the potential to accelerate bone healing when applied to injured tissues or surgical sites [4].

Hyaluronic Acid (HA) is a high-molecular-weight linear polymer made up of two repeating disaccharide subunits of N-acetylglucosamine and D-Glucuronic acid, an important component of the periodontal ligament matrix since it forms the basis of the extracellular matrix. Various HA binding proteins and cell surface receptors, such as CD44, play a key role in cell adhesion, motility, and differentiation [5]. In Gingival Crevicular Fluid (GCF), HA has been explored as a potential metabolite, a key marker of inflammation, as well as a pivotal factor in tissue repair and renewal [6]. Hyaluronan, a synthetic version, is available in gel or liquid form for oral and periodontal applications [7].

Hyaluronan plays a role in the migration and adhesion of polymorphonuclear leukocytes and macrophages to the inflamed region, as well as the phagocytosis and destruction of invading microorganisms [7]. Hyaluronan accelerates cell proliferation, matrix cell migration into the granulation tissue, and granulation tissue maturation and remodelling during healing. Hyaluronan production is transiently enhanced in extracellular matrix during granulation tissue formation and re-epithelialisation. HA in healing tissues is gradually replaced by a provisional mineralised callus during granulation tissue development [8]. Osteogenic proteins including bone morphogenetic protein-2 and osteopontin have bone induction properties with HA [9]. A 0.8% HA gel (Gengigel) has been used both in non surgical and surgical periodontal disease management effectively [10,11].

One of the most prevalent and promising calcium compounds for use as a bone graft alternative is beta tricalcium phosphate. The ß-TCP is a resorbable material with 99% phase purity, total microporosity, and a homogeneous ceramic sinter structure [12]. The intergranular spaces act as a scaffold for blood vessel ingrowth, which provides nutrients

to the newly developed bone structures. The delayed biodegradation feature ensures that it is entirely digested, harmonises with bone growth, remodelling, and results in the material being displaced to bone [13]. The ß-TCP has been widely used in periodontal regeneration [14,15]. To our knowledge, HA in conjunction with β-TCP is being analysed in intrabony defect management for the first time.

Therefore, the present study aimed to assess the clinical efficacy of 0.8% HA with β-Tricalcium Phosphate (β-TCP) in the treatment of intrabony periodontal defects.

MATERIALS AND METHODS

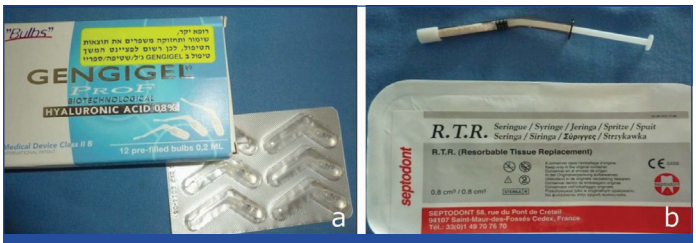
This prospective clinical study was conducted , from January 2017 and December 2017 (followed-up to June 2018), at the Department of Periodontics, SRM Dental College, Chennai which was duly approved by the Institutional Ethical Committee (SRMDC/IRB/MDS/No.506).

Sample size calculation: The sample size was estimated using G power software a proportion of 0.15, a Type II error of 90%, and a Type I error of 5% [16]. The estimated sample size was 12 sites in each group.

Inclusion and Exclusion criteria: Isolated sites with Probing Pocket depth (PPD) ≥5 mm (following root surface debridement) having a two or three walled intrabony defect in the posterior teeth were included in the study. Smokers, pregnant women, patients with systemic disease/condition influencing course of periodontal disease (diabetic patients, chronic systemic diseases such as rheumatoid arthritis, renal, hepatic and pulmonary diseases; allergies and patients who underwent periodontal treatment in past six months and those taking medications (corticosteroids or bisphosphonates) influencing bone metabolism were excluded from the study.

Study Procedure

Thirty sites (15 in control and test group each) from 16 systemically healthy patients (nine females and seven males) diagnosed with chronic periodontitis. Both localised and generalised chronic periodontitis patients with age ranging from 25-55 years were recruited. Test group (15 sites) had seven maxilla and eight mandible sites, where as control group (15 sites) had six maxilla and nine mandible sites. Informed consent was obtained based on the declaration of Helsinki. The selected sites were randomly divided into two groups using envelope method: test and control. The test sites received 0.8% HA (Gengigel® Prof. Bulbs, Ricerfarma, Italy) and β-TCP (Septodont RTR®, France) [Table/Fig-1a,b] whereas the control sites received only β-TCP.



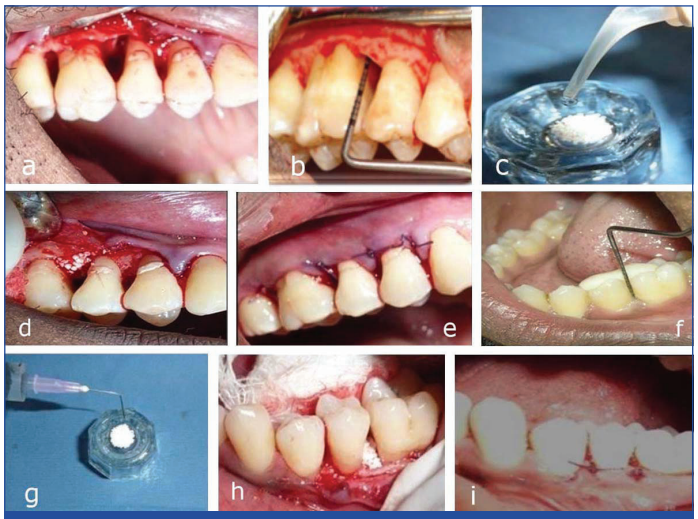
[Table/Fig-1]: Biomaterials used in the surgical management. a) Gengigel bulbs 0.8% Hyaluronic Acid (HA); b) Septodont Resorbable Tissue Replacement β-TCP.

Clinical and radiographic assessment: The clinical parameters studied were Probing Pocket depth (PPD) and Clinical Attachment Level (CAL), the radiographic parameter analysed was the bone defect level.

A single investigator used the University of North Carolina 15 probe (UNC 15, Hu Friedy, USA) with acrylic stents to record PPD, CAL level at baseline, three and six months review. The distance between the Cementoenamel Junction (CEJ) and the base of the sulcus was used to calculate the CAL. For all teeth, probing depth and CAL were recorded at six sites.

For radiograph standardisation, the guiding arm was attached to the cone-positioning unit (Xcp-Ds, Gendex, Dentsply), to engage the head of the tube while exposure, and a number 1 adult E-speed film (Carestream Dental E speed) was placed in an Intraoral Periapical (IOPA) film holder with bite plane and the patient's bite was registered with acrylic in order to reproduce it at the follow-up. Using an HP transparency positive scanner, all of the radiographs were scanned and digitalised. The scanned photos were shown on a monitor, and linear measurements were taken with Adobe Photoshop Computer Software (CS2) from Adobe Systems using CEJ/margin of restoration and deepest point of alveolar crest as the reference points [17].

Surgical procedure: Following administration of 2% local anaesthesia with 1:80000 adrenaline, sulcular incisions with scalpel using 15c blade were placed in the surgical area, and elevation of a buccal and lingual/palatal mucoperiosteal flap was done (Kirkland flap). Root surface/defect debridement was performed with Gracey curettes. After proper isolation of defect, a mixture of 0.5 CC of β-TCP (Septodont, rue du Pont de Creteil, France) and bulb dispensing 0.2 mL of 0.8% HA (Gengigel, Ricerfarma, Milan, Lombardy, Italy) graft placed in the defects in test group and β-TCP hydrated with saline were placed in the control group. Graft was filled upto the crest of the alveolar bone. Flap closure was obtained with 4-0 vicryl simple interrupted suture and a Periodontal dressing (COE-PAK) was placed to protect the surgical site [Table/Fig-2a-i].



[Table/Fig-2]: Surgical management of cases. a) Flap elevation and defect debridement (test) in relation to 15,16; b) Depth of defect in 15,16; c) β-TCP + HA preparation; d) β-TCP + HA placement; e) Flap approximation; f) In relation to 35, 36 (Control); g) β-TCP + saline preparation; h) Flap elevation and graft placement β-TCP (test) in relation to 35,36; i) Flap approximation.

Postoperative care: Patients were prescribed amoxicillin and clavulonic acid 625 mg thrice daily for five days along with Ibuprofen 400 mg and paracetamol 325 mg combined analgesics for three days. For two weeks, oral hygiene maintenance with chlorhexidine (0.12%) mouthwash was prescribed. To avoid trauma to the surgical site, patients were told not to brush the region for two weeks after surgery. After two weeks, the dressing was removed, and sutures were removed in relation to the defect-related site and irrigated with saline.

All patients were recalled for follow-up visits at the end of the second week, the three month, and the six month after surgery. At the end of three and six months, clinical data were documented. Radiographic measurements were taken at baseline and at the end of six months.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS) version 22.0 was used to analyse the data. Site level statistical analysis was carried out. The descriptive parameters were expressed in terms of mean and standard deviation. The Mann-Whitney U test was used for intergroup comparisons and Wilcoxon-Signed Rank test was used for intragroup comparison at the various study points as the

data were non parametric. Values were considered as statistically significant if p-value <0.05.

RESULTS

There were 30 sites in total, divided into two groups with 15 sites in the test group and 15 sites in the control group. Data was obtained at three points: at the start of the surgery (baseline), three months later, and six months later. The mean age of the control and test groups was 45.7 and 48.5 years respectively.

Throughout the study, all patients maintained satisfactory plaque control, plaque index and gingival index scores were 0.88±0.41, 0.90±0.40 and 0.75±0.42, 0.76±0.41 at six months in the test and control groups, respectively.

The PPD was reduced and CAL and bone fill were increased in both study groups from baseline, indicating clinical effectiveness [Table/Fig-3]. From baseline to six months, the PPD reduction and gain in CAL in the test and control groups were 3.27±0.18 mm, 3.20±0.18 mm and 3.07±0.03 mm, 3.07±0.08 mm, respectively, which was statistically significant (p-value <0.001) [Table/Fig-3].

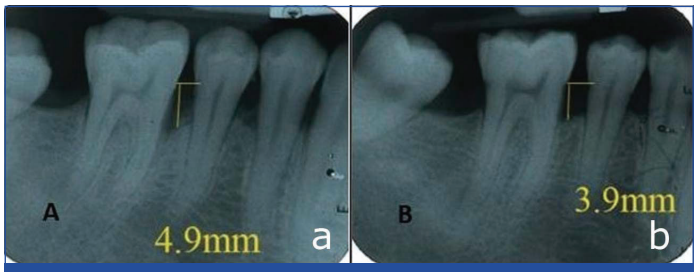
In both groups, the bone defect level was statistically reduced from baseline to six months with a mean difference of 1.37±0.36 mm and 1.43±0.03 mm in the test and control group respectively (p-value <0.001) [Table/Fig-3]. Intergroup comparison revealed no statistical significance (p-value >0.05) in both clinical (PPD, CAL) and radiographic parameters {Bone Defect Depth (in mm)} [Table/Fig-4]. [Table/Fig-5] shows the preoperative and postoperative radiographs in test and control sites demonstrating the bone fill.

Clinical and radiographic parameters	Test group			p-value	Control group			p-value
	Baseline-3 months	3 months-6 months	Baseline-6 months		Baseline-3 months	3 months-6 months	Baseline-6 months	
PPD (in mmm)	2.13±0.13	1.13±0.19	3.27±0.18	<0.001**	2.13±0.08	0.93±0.05	3.07±0.03	<0.001**
CAL (in mm)	2.13±0.03	1.07±0.36	3.20±0.18	<0.001**	2.13±0.01	0.93±0.09	3.07±0.08	<0.001**
Bone defect depth (in mm)	-	-	1.37±0.36	<0.001**			1.43±0.04	<0.001**

[Table/Fig-3]: Intragroup comparison of the parameters between different time intervals among control and test sites.
Wilcoxon Signed Rank test was used for Intragroup comparison; **p-value <0.001 was considered statistically significant

Clinical and radiographic parameters	Baseline				3 months				6 months			
	β-TCP (control)	β-TCP + HA (test)	Mean Diff (mm)	p-value	β-TCP (control)	β-TCP + HA (test)	Mean Diff	p-value	β-TCP (control)	β-TCP + HA (test)	Mean Diff	p-value
PPD (in mm)	7.07±0.88	7.20±1.21	-0.133	0.88	4.93±0.80	5.07±1.22	-0.133	0.84	4.00±0.85	3.93±1.03	0.067	0.74
CAL (in mm)	7.13±1.30	7.60±2.10	-0.467	0.61	5.00±1.31	5.47±2.13	-0.467	0.75	4.07±1.22	4.40±1.92	-0.333	0.85
Bone defect level (in mm)	5.61±1.54	5.41±1.95	0.207	0.56	Not determined				4.18±1.51	4.04±1.59	0.140	0.775

[Table/Fig-4]: Intergroup comparison of the clinical and radiographic parameters at all study points.
Mann-Whitney U test was used for intergroup comparisons statistical significance at p-value <0.05, ß-TCP: Beta tricalcium phosphate; HA: Hyaluronic acid; PPD: Probing pocket depth; CAL: Clinical attachment level; Not determined: Radiographic changes are markedly appreciable only after 6 months; p-value <0.05 was considered significant



[Table/Fig-5]: Radiographs showing defect fill. Additional radiographs which could be retrieved are below: a) Test Site (preoperative and postoperative); b) Control site (preoperative and postoperative)

DISCUSSION

The ultimate aim of periodontal therapy is periodontal tissue regeneration. Currently, the two procedures with histological proof of periodontal regeneration are osseous grafting and guided tissue regeneration [18]. The goal of using bone grafts is to change the biological response to a regenerative rather than a largely reparative pattern of periodontal healing. In the present study, 16 systemically healthy patients with 30 intrabony defects were randomly randomised to receive either HA plus β-TCP or β-TCP alone. Clinical and radiographic indicators were used to evaluate the efficacy of HA in human intrabony abnormalities.

In the control group of the present study, the mean difference of reduction in PPD was 3.07 mm from baseline to six months which was statistically significant (p-value <0.001) and a mean difference of 3.07 mm gain in CAL was observed from baseline to six months (p-value <0.001). The results were in concordance to those noted by Özdemir B and Ökte E who found a mean PPD reduction of 3.0 mm in the β-TCP group and a gain in CAL of 2.0 from baseline to six months while examining the therapeutic efficacy of β-TCP and Platetelet Rich Plasma (PRP)/β-TCP combination [19]. In yet another similar study, Pinipe J et al., found a substantial mean reduction in PPD of 2.80 and a significant gain in CAL of 2.60 at six months follow-up with β-TCP (Septodont) while comparing the clinical effect of β-TCP alone and in conjunction with PRP [20].

In the current study, a statistically significant mean bone fill of 1.43 mm was detected in control sites treated with TCP at six months, which was consistent with Stavropoulos A et al., study, wherein they observed a mean new bone fill of 1.0±0.7 mm from baseline to six months after placing granular β-TCP following open flap debridement [21]. β-TCP was reported to be effective in intrabony defect management by Nevins M et al., and Saffar JL et al., [22,23]. Furthermore, Nevins M et al., affirmed that as β-TCP is resorbed over several months, it would not obscure the bone fill, resulting in CAL increase and a reduction in intrabony defect depth on radiograph [22].

On the other hand, the mean difference in reduction of PPD and the mean difference of gain in CAL among test subjects was 3.27 mm and 3.20 mm at six months follow-up, respectively which were statistically significant (p-value <0.001). In a study by Bogaerde V, esterified HA was used to treat 19 deep periodontal defects and achieved an attachment gain of 3.8 mm at one year review which was comparable to the CAL gain (3.20 mm) achieved in this study [24]. In the current study, mean bone fill of test group from baseline to six months was 1.37 mm which could not be compared with other studies due to the lack of scientific literature using the combination of HA and β-TCP in management of intrabony defects.

However, Engström PE et al., in an experimental model, treated defects on the test side with resorbable membrane and HA and observed a 0.5 mm increase in bone height on the test sites [25]. Baldini A et al., assessed the potential of HMW HA (Hyaloss TM matrix) as an organic scaffold for bone repair in postextaction

defects and found that the bone deposit process was accelerated [26]. Ballini A et al., also investigated the osteoinductive activity of HA as an adjuvant to autologous bone derived from intraoral locations in the treatment of intrabony defects and suggested that autologous bone mixed with HA appears to have a reduction in the depth of pockets as well as a significant reduction in epithelial/lymphocyte cell proliferation and great potential in stimulating new bone formation in intrabony defects [27].

Joint fluid, umbilical cord, rooster comb, and particular strains of streptococci have all been used to isolate and synthesise HA. The tissue half-life of HA ranges from 12 to 36 hours, depending on the route of removal. In humans, it is efficient at reducing inflammation [27].

Pistorius A et al., and Jentsch H et al., recommended the use of a Hyaluronan-containing gel, which they found to be effective in treating plaque-induced gingivitis [28,29] and Xu Y et al., investigated the use of 0.8% hyaluronan as an adjunctive therapy following mechanical debridement and found positive results [30].

In an animal model, Aslan M et al., suggested that HA requires an osseoconductive scaffold to produce good bone growth in crucial size defects [31]. Various authors have described the dose dependent activity of HA and recommended that 0.2% is effective in gingivitis, 0.8% is used along with mechanical debridement and 1% may be used to accelerate healing in tooth sockets, healing bone in critical sized defects [29,32-34]. In a recent animal study by Chang YL et al., enhancement in bone healing was noted while using HA and hydroxyapatite/β-Tricalcium Phosphate in combination [35]. On the contrary, the addition of HA to Biphasic Calcium Phosphate did not significantly promote bone repair at four and 10 weeks in another animal model by Ahmed AG et al., [36].

The current study targeted on exploring the regenerative potential of 0.8% HA by assessing the clinical, radiographic outcomes. However, the results did not show any additional therapeutic benefit of using HA in combination with β-TCP.

Limitation(s)

The radiographic confirmation of bone fill was not proficient enough to distinguish between new bone and the bone graft. Further long term studies with a bigger sample size are warranted to substantiate the efficacy of HA as an adjunct to β-TCP in periodontal regeneration.

CONCLUSION(S)

Within the scope of the study, authors were unable to demonstrate improved effects using HA as an adjuvant to β-TCP in test sites despite both test and control sites having significant bone fill and clinical attachment gain compared to baseline.

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