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ORIGINAL ARTICLE

Prospective randomized controlled clinical trial to compare hard tissue changes following socket preservation using alloplasts, xenografts vs no grafting: Clinical and histological findings

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Abstract

Purpose: To compare dimensional changes and bone quality of two different grafting materials used for socket preservation.

Materials and Methods: Thirty-three patients requiring extraction were recruited and randomly assigned to receive: biphasic calcium sulfate/ hydroxyapatite (BCS/HA); bovine derived xenograft (BDX) or no grafting (Control). Ridge width (at −3 and −6 mm) and vertical distance from a stent were measured at the time of extraction/grafting. Measurements were repeated at reentry and core biopsies were harvested.

Results: Baseline vertical distance for the BDX, C and BCS/HA groups were 7.45 ± 3.1, 7.69 ± 4.2, and 6.75 ± 3.5 mm, respectively (P = .830). Post-op, C group had greater vertical loss (1.71 ± 0.4 mm) compared to BCS/HA (0.65 ± 0.5) and BDX (0.25 ± 0.2 mm), P = .059. Mean baseline width at −3 mm was 8.69 ± 1.1 mm, 8.31 ± 1.4 mm, and 9.0 ± 1.1 mm, respectively (P = .509). Post-op, this width was reduced by 2.96 ± 0.3 mm (C), 1.56 ± 0.4 mm (BDX), and 0.5 ± 0.4 mm (BCS/HA), P = .001. Mean ridge width at −6 mm for the C (6.5 ± 1.7 mm) was significantly smaller than BCS/HA (7.95 ± 2.8 mm) and BDX (8.85 ± 1.9 mm), P = .043. Histologically, the BDX group had greater residual scaffold material and less vital bone compared to the BCS/HA group. Pain scores were relatively low for all groups.

Conclusions: BCS/HA may be used for socket preservation with similar or better results compared to BDX. The significance of greater residual scaffold found in the BDX group is yet to be determined.

KEYWORDS

alloplasts, bone grafts, extraction, natural healing, regeneration, socket preservation, xenografts

1 | INTRODUCTION

Tooth extraction is associated with remodeling of the alveolar process in the extraction socket and results in both structural and dimensional changes. A horizontal bone loss of 29-63% and a vertical bone loss of 11-22% is expected at 6 months following tooth extraction.[1] This phenomenon may compromise the restoration of missing teeth with dental implants. To overcome this impediment, the concept of socket preservation aimed at minimizing bone resorption following tooth extraction, was developed.[2] Animal and human studies have shown that bone substitutes such as human demineralized bone matrix, deproteinized bovine bone mineral, magnesium-enriched hydroxyapatite, and others are effective materials for ridge preservation.[3] In a recent meta-analysis, Iocca and colleagues (2017) reported statistically significant results favoring the grafted sockets compared to non-grafted sites for both vertical (mean differences of 1.02 mm) and

horizontal (mean difference of 1.52 mm) bone loss.[4] Statistically significant differences could not be found between various treatment alternatives or bone substitute materials.[5]

In the context of bone substitutes, calcium sulphate is a well-established grafting material that has been used for decades in orthopedics and oral surgery. It has been shown to be well tolerated with a rapid turnover associated with subsequent bone regeneration.[6] Calcium sulphate in extraction sockets has been shown to completely resorb and allows for new trabecular bone to form.[7]

A potential downside of calcium sulphate is its rapid resorption rate. Hydroxyapatite (HA) is the most stable calcium phosphate salt. It has a slow resorption rate in a physiological environment. The use of a second phase additive with a faster degradation rate as the composite component, for example, tri-calcium phosphate, calcium carbonate or calcium sulphate etc., is considered a simple method to regulate the degradation rate of HA based materials as the degradation increases with an increased amount of additives.[8] The combination of calcium sulphate and HA particles might be potentially beneficial as the material transforms into bone throughout the entire volume and not only by creeping substitution, from the surface towards the center.[9] This combination also displays good initial volume stability and strength.[10] A previous canine study published by our group demonstrated its efficacy in dehiscence type extraction defects.[11] Furthermore, a human clinical trial found superior results when compared to natural healing of extraction sockets in terms of horizontal dimensional changes after 4 months of healing.[12] De Rosi and colleagues[13] in a systematic review and meta-analysis of histomorphometric results with various grafting materials for socket preservation, reported a large variation in the amount of new bone formation between the various grafting materials, however none were shown to be statistically superior over the other. Comparative studies of calcium sulphate /HA Alloplasts and bovine derived xenografts (BDX) for socket preservation are scarce.

Thus, the aim of the present randomized controlled clinical trial was to examine the dimensional changes following tooth extraction and to compare (clinically and histologically) different grafting materials for socket preservation.

Specific aims: (1) To compare changes in ridge width and height between the groups and (2) to assess and equate the healed bone quality in the grafted sights.

2 | MATERIALS AND METHODS

The study was initially approved by the Rambam health care campus Helsinki committee (RMB #092-15; ClinicalTrials.gov Identifier: NCT02440048) and conducted in the Department of Periodontology, School of Graduate Dentistry at this center (June 16, 2015 until November 30, 2017). Patients in need for nonmolar tooth extraction were recruited for this prospective randomized clinical trial provided that they met the following inclusion criteria: Age above 18 years; nonmolar tooth requiring extraction, prospectively scheduled for implant placement 4-6 months later.

Exclusion criteria: patients taking bone-sparing medications; pregnant or lactating women; heavy smokers (>20 cigarettes per day) and patients wearing tissue supported removable dentures. Also, patients with systemic conditions that might affect wound healing were excluded as per the clinicians' discretion.

Sample size was initially calculated (10 or more patients in each group); consequently, thirty-three patients were initially recruited. Prior to tooth extraction, patients were randomized into one of the treatment groups using a computer-generated block randomization list. The entire process including patients' allocation was performed by the study coordinator that was not involved in the patients' management in any way. Furthermore, the patient and the clinician responsible for the clinical measurements were both blinded to the nature of the treatment that was rendered.

I. Socket preservation using biphasic calcium sulfate with hydroxyapatite (Bond-apatite, Augma Biotech, Netanya, Israel)—BCS/HA group (n = 11).
II. Socket preservation using bovine derived xenograft (Bio-Oss, Geistlich, Wolhusen, Germany)—BDX group (n = 11).
III. Tooth extraction without socket preservation—Control group (n = 11).

Next, the tooth was extracted as atraumatically as possible with minimal reflection of the surgical flaps. A thorough debridement of the socket was completed and clinical measurements were performed using an omnivac or acrylic stent that was prepared and marked at the experimental sites (Figure 1).

- Horizontal width of the alveolus at −3 and −6 mm apically from the crest (primary outcome variable) using a standard caliper with 0.1 mm marking (Medesy, Maniago, Italy) was measured.
- Vertical distance from the inferior border of the stent to the bone crest (V-distance) using a UNC 15 mm probe was measured.
- Residual walls width (of the sockets) at −3 and −6 mm apically from the corresponding buccal and lingual crests (WW-3 and -6) were measured.

Once measurements were completed, the sockets were grafted with either xenografts (BDX group) or alloplasts (BCS/HA group) or left for the blood clot to fill the void (Control), Figure 2A,F.

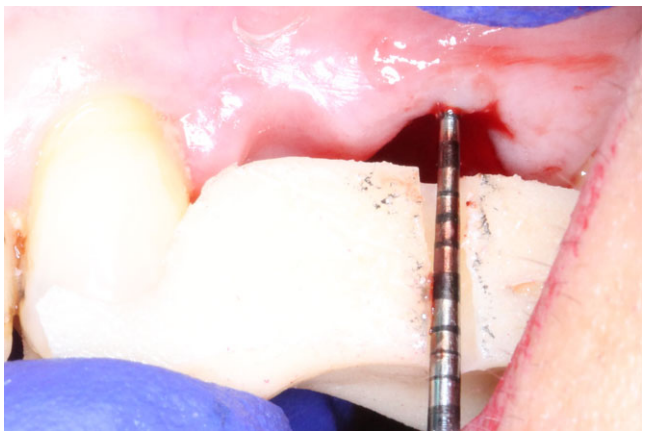

FIGURE 1 Stent was grooved to ensure repeatability of the measurements

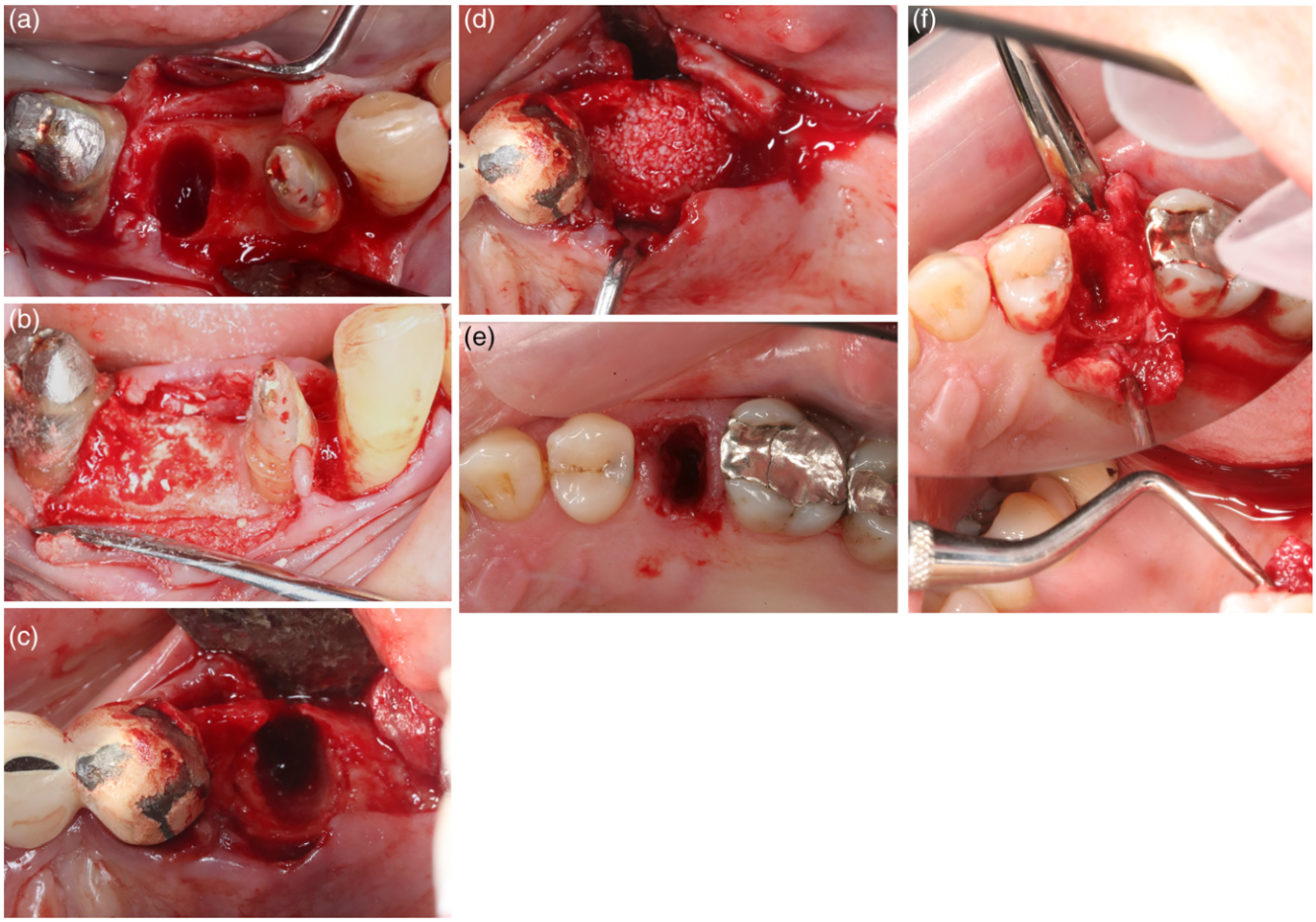

FIGURE 2 Atraumatic extraction of tooth #29 (A), socket was filled with BCS/HA that was lightly condensed (B). Tooth #13 was extracted (C), following debridement the socket was filled with BDX with slight overfill (D). In another patient, tooth #13 was extracted (E), flaps were raised but grafting material was not placed (F), flaps were approximated to contain the blood clot

Flaps were than approximated to contain the grafting materials and to secure the blood clot. Post operatively, antibiotics were prescribed (1.5 g/day of amoxicillin with clavulanic acid or 600 mg/day clindamycin) for 1 week and a nonsteroidal analgesic medication (naproxen-sodium 275 twice daily) for 3 days. Patients were instructed to rinse twice daily starting on the second day, with CHX 0.2% twice a day for 2 weeks, at which time they were seen for suture removal. At that time, patients were asked to assess their postoperative pain level using a visual analog scale (VAS).[14] Patients were further followed at weeks 4, 8, and 12. Final surgical measurements were repeated at the time of implant placement scheduled at 4 months post-op.

At the time of implant surgery, core biopsies were obtained from the center of the previous socket site using a 2 mm ∅ trephine drill, followed by completion of the osteotomy and implant installation; the samples were immediately placed into a 4% formalin solution.

2.1 | Histology and histomorphometry

Specimens were stored in 4% paraformaldehyde for 2 days. Fixed specimens were decalcified for 2 days in Calci clear rapid (National diagnostics, CA), embedded in paraffin, sectioned (8 μm) and stained with Hematoxylin and Eosin (H&E). Histological slides were captured by a digital camera (Olympus DP70, Olympus, Tokyo, Japan) with a calibration scale and analyzed morphometrically using imageJ software (NIH, Bethesda, MD). Histomorphometric measurements were performed by one blinded examiner and included calculation of the percentage of residual scaffold, bone, and connective tissue.

2.2 | Statistical analysis

Following normality test, a paired Student's *t*-test was used to compare the clinical variables between baseline and reentry. Changes in the vertical and horizontal dimensions around these sockets following tooth extraction, histomorphometric data and pain scores, were compared between the groups using a one-way analysis of variance. A 5% significance threshold was used.

3 | RESULTS

Thirty-three subjects were initially enrolled into the study. Ages ranged from 45 to 80 years, mean 63.9 ± 8.1 (median, 64 years). Few (n = 2) of these patients were current smokers while seven were past smokers; thus the majority of the patients (n = 24) never smoked. Males (n = 21) significantly outnumbered females (n = 12) in this study population. Premolar teeth (n = 29) were the most common tooth type requiring extraction followed by two canines and two

TABLE 1 Changes in sites parameters—comparison between groups

Variable	BDX group[a]	Control	BCS/HA group[b]	*P*-value[c]
Vertical distance (stent-crest)-pre	7.45 ± 3.1	7.69 ± 4.2	6.75 ± 3.5	.830
Vertical distance (stent-crest)-post	7.7 ± 3.1	9.88 ± 3.6	7.40 ± 3.0	.171
Δ vertical distance (stent-crest)	0.25 ± 0.2[d]	1.71 ± 0.4	0.65 ± 0.5[d]	.059
Crest width (at −3 mm), pre	8.69 ± 1.1	8.31 ± 1.4	9.0 ± 1.1	.509
Crest width at (−3 mm), post	7.25 ± 1.9[d]	5.35 ± 1.2	8.57 ± 1.0[d]	.000
Δ crest width (at −3 mm)	1.56 ± 0.4[d]	2.96 ± 0.3	0.50 ± 0.4[d,e]	.001
Crest width (at −6 mm), pre	9.50 ± 1.4	8.30 ± 1.9	8.68 ± 1.8	.327
Crest width at (−6 mm), post	8.85 ± 1.9[d]	6.50 ± 1.7	7.95 ± 2.8[d]	.043
Δ crest width (at −6 mm)	0.56 ± 0.4	1.81 ± 0.3	0.81 ± 0.4	.197

[a] Bio-Oss, Geistlich, Wolhusen, Germany.
[b] BondApetite, Augma Biotech, Netanya, Israel.
[c] Analysis of variance.
[d] Significantly different from control.
[e] Significantly different from BDX & C.

incisors. Both mandible and maxilla was evenly represented (n = 16 and n = 17 respectively). Mean buccal plate immediately after extraction was 1.18 ± 0.54 and 1.55 ± 0.73 mm (at −3 and − 6 mm from the crest) while the lingual plates were significantly thicker (1.96 ± 0.91 and 2.65 ± 1.15 mm) at −3 and −6 mm from the crest respectively. One patient (C group) dropped out from the study due to a nonrelated medical condition therefore there was a 97% retention rate. Most sites were reentered at the scheduled 4 month appointment, however few sites (0-2 in each group) were reentered at up to 6 weeks later (mean reentry visit at 4.5 ± 0.4 months).

Dimensional changes in the three treatment groups are presented in Table 1. Mean (±SD) vertical distance (stent-bone crest) at baseline was similar in all groups: 7.45 ± 3.1, 7.69 ± 4.2, and 6.75 ± 3.5 mm for the BDX, C and BCS/HA groups respectively (P = .830). Following tooth extraction, the C group had greater crestal bone loss (1.71 ± 0.4 mm) compared to the BCS/HA (0.65 ± 0.5 mm) and BDX (0.25 ± 0.2 mm) groups (P = .059).

Mean (±SD) horizontal width 3 mm apical to the bone crest was similar at baseline for all groups: 8.69 ± 1.1, 8.31 ± 1.4, and 9.0 ± 1.1 mm for the BDX, C and BCS/HA groups respectively (P = .509). Following tooth extraction, the C group had the greatest horizontal bone loss (2.96 ± 0.3 mm); the BDX group exhibited only half of these dimensional changes (1.56 ± 0.4 mm) while the BCS/HA group had minimal changes (0.5 ± 0.4 mm), which was significantly smaller than both other treatment groups, P = .001 (Figure 3). Finally, the mean baseline horizontal width 6 mm apical to the bone crest was

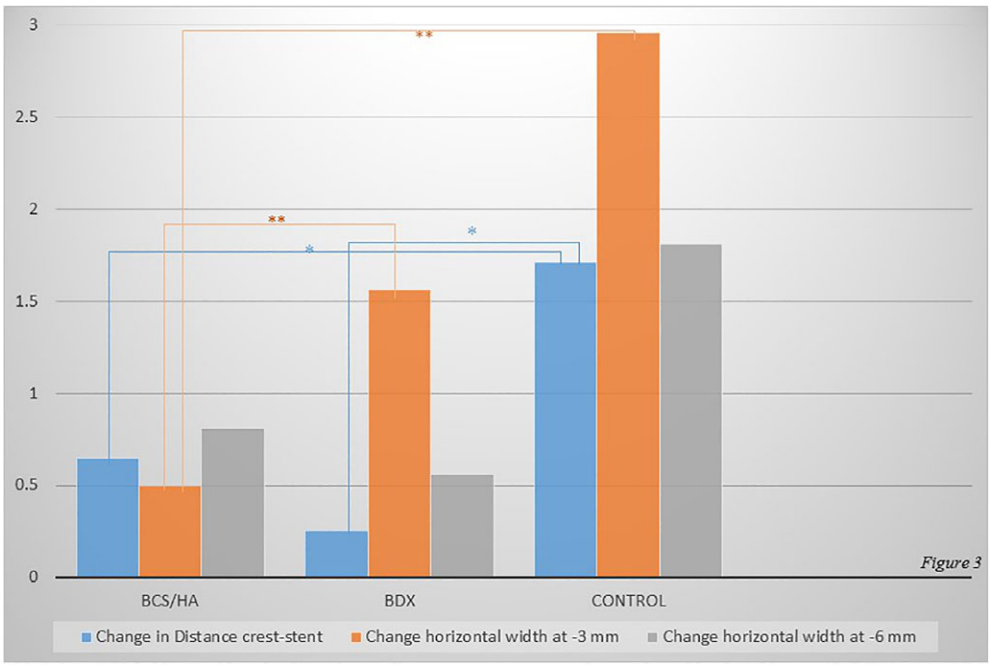

FIGURE 3 Clinical changes: BCS/HA group demonstrated the smallest changes (0.5 mm) ridge width at −3 mm while the control group exhibited the greatest change (2.96 mm). Vertical bone loss was smaller in both experimental groups (0.65 and 0.25 mm, respectively) while greatest in the control (1.71 mm)

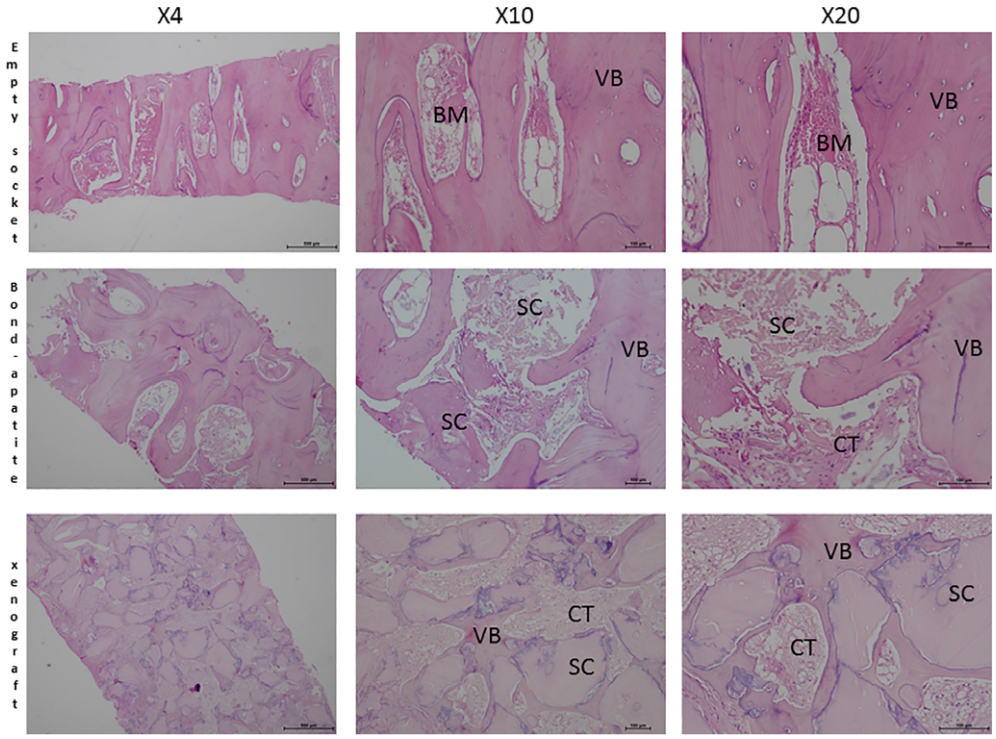

FIGURE 4 Representative images of histological slides obtained from the sockets of the nongrafted controls (top raw), BCS/HA (middle) and BDX groups (bottom). Slides were stained with H&E and observed with a light microscope at ×4, ×10, and ×20 magnification (Nikon ECLIPSE Ts2R). Vital bone (VB), surrounded by connective tissue (CT) was considerably higher in the control group, while least visible in the BDX. Residual scaffold material (SC) was visible in both grafted groups but more so in the BDX group

similar for all groups: 9.5 ± 1.4, 8.3 ± 1.9, and 8.68 ± 1.8 mm (P = .327), at reentry the mean width for the C group (6.5 ± 1.7 mm) was significantly smaller than the BCS/HA (7.95 ± 2.8 mm) and the BDX (8.85 ± 1.9 mm) groups (P = .043).

Mean buccal plate thickness at −3 mm was similar for all three groups: 1.1 ± 0.7, 1.21 ± 0.6, and 1.2 ± 0.3 mm for the BCS/HA, BDX and C groups respectively (P = .905). The widths for the same groups at −6 mm was also similar: 1.28 ± 0.6, 1.55 ± 0.6, and 1.71 ± 0.8 mm for the BCS/HA A, BDX and C groups respectively (P = .492). Likewise, the width of the lingual plate at −3 mm was somewhat greater than that of the buccal plate and was similar in all groups: 1.9 ± 1.2, 2.18 ± 0.7, and 1.83 ± 0.8 mm for the BCS/HA, BDX and C groups respectively (P = .666). The widths for the same groups at −6 mm were also similar: 2.86 ± 1.5, 2.65 ± 1.0, and 2.51 ± 1.0 mm for the BCS/HA A, BDX, and C groups, respectively (P = .798).

Microscopic examination of the specimens revealed vital bone in all groups which was characterized by the presence of blood vessels and osteocytes (Figure 4). Samples obtained from patients in the BDX and BCS/HA groups presented variable amounts of residual graft surrounded by bone. None of the samples demonstrated heavy inflammation, however slight inflammation was occasionally found in the connective tissue in the more coronal part near the crestal bone. Histomorphometric analysis of the core biopsies (Figure 5) revealed that the percent of bone in the C group (81.72 ± 4.3%) was substantially and significantly (P = .000) greater than that in the BCS/HA group (44.15 ± 18.8%) which, in turn, was greater than in the BDX group (22.50 ± 24.72%) and was bordering significance (P = .07). The proportions of the residual scaffold in the BDX group (40.18 ± 17.2%) were significantly greater than in the BCS/HA group (16.51 ± 16.2%), P = .012.

Pain scores were relatively low (mean = 3.14 ± 0.55). Slightly lesser pain was reported in the control group (2.29 ± 0.88 SE) compared to the BCS/HA (3.13 ± 1.0) and BDX (4.00 ± 0.97) groups, however these differences did not reach statistical significance (P = .486).

4 | DISCUSSION

Both BCS/HA and BDX groups resulted in less vertical and horizontal bone loss following tooth extraction when compared to the nongrafted control. Toloue[15] utilized a calcium sulphate (CS) bone graft and reported somewhat greater horizontal bone loss (−1.33 mm) as compared to 0.5 mm in the present study, with comparable and minimal vertical bone loss. Willenbacher and co-workers[16] in a systematic review and meta-analysis of socket preservation reported that the weighted mean differences between grafted and nongrafted sites were 1.31-1.54 mm in the horizontal direction and 0.91-1.12 mm in the vertical direction. In comparison, in the present study, the differences in the vertical direction were somewhat smaller (0.4 mm) and the differences in the horizontal direction were somewhat greater (1.0-2.46 mm). Thus, the results obtained in the present study are comparable with previously published research.

Several studies have compared BDX with other alloplasts and achieved mixed results: Shakibaie[17] compared BDX with silicon dioxide/HA grafting materials for socket preservation. They reported that

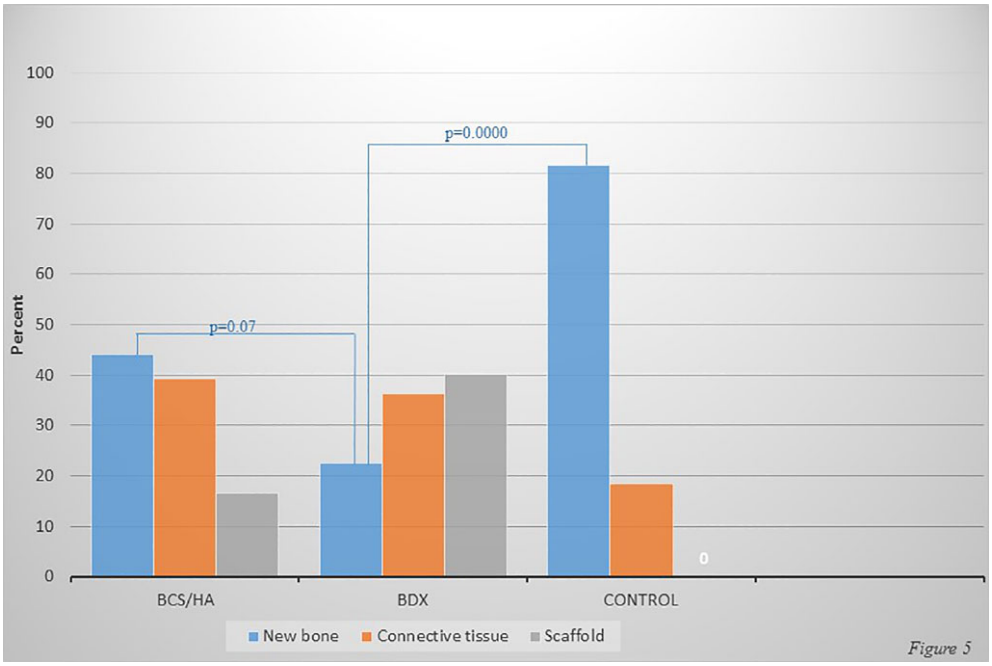

FIGURE 5 Histomorphometric results: percentage of new bone in the control (81.5%) was significantly greater than BCS/HA (44.4%) which in turn was almost double than that in the BDX group (21.5%). On the contrary, BDX had greater proportions of residual scaffold material (44.18%) compared to the BDX group (16.51%)

the dimensions of the ridge at the extraction site were better preserved in the BDX group compared to the silicon dioxide/HA or nongrafted sites. Conversely, Kotsakis and colleagues[18] in a similar human study of socket preservation, reported that the CS and the BDX treated groups had comparable dimensional changes that were better than in the nongrafted group. Likewise, Gholami and co-workers[19] in a similar study compared BDX with synthetic nanocrystalline HA reported comparable results with both materials. These differences may be attributed to the different alloplasts that were utilized in these studies, each with its specific physical, chemical and therefore biological properties. Finally, Atieh and colleagues[20] in systematic review and meta-analysis of only RCTs of at least 6 months' duration, found only two papers that compared alloplasts vs xenografts with no evidence that either ridge preservation techniques caused a smaller reduction in ridge height or width.

All sites healed with new bone and connective tissue. Residual scaffold material was significantly greater in the BDX group (40.18%) than the BCS/HA group (16.51%), $P = .021$. Percent bone in the BCS/HA group (44.15%) was twice that of the BDX group (22.50%). Toloue[15] in a socket preservation study in humans found somewhat smaller proportions of vital bone (32%) when using CS, but significantly less residual scaffold (2.5%). Canullo and colleagues[21] reported an accelerated new bone formation: from 15.0% at 2 months to 77.4% at 4 months after socket preservation with CS. In a similar study using BDX, Norton[22] reported 26.9% new bone 25.6% residual graft material. Finally, Gholami[19] in a comparative histomorphometric study reported, comparable to our study, 27.3% vital bone fraction for the BDX, however smaller proportion (28.6%) for the nano-crystalline/HA group compared to 44.5% for the BCS/HA group in the present study. Again, the heterogeneity in the various alloplastic materials might be responsible for the variability in the histological treatment outcomes.

A possible drawback of this study is the relative small sample size. Yet, the results for the BDX group and the C group are similar to previous studies, thus suggesting that this might not be of a major concern. Also, barrier membranes, sometimes used in-conjunction with socket preservation procedures, were not used in the present study. Thus, the conclusions of this study pertain only to bone grafts used as a stand-alone procedure.

All patients reported low to moderate pain level following surgery ranging from 0 to 5 on the VAS (mean 3.14 ± 0.55) which was similar amongst the three groups. Very few studies reported on patient centered outcomes following socket preservation. Mozzati and colleagues[23] reported, following socket preservation procedure with biomimetic nanostructured matrix that patients reported pain scores were ≤4. Most recently (2018) Martin-Thome and colleagues[24] in a private practice setting, using a barrier membrane for socket preservation and bone augmentation, reported very similar pain scores (mean 2.2).

5 | CONCLUSIONS

BCS/HA may be used as the material of choice for socket preservation with similar and sometimes even better results compared to BDX. The significance of the greater residual scaffold found in the BDX group on implant placement in these sites is yet to be determined.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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