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HUMAN RANDOMIZED CONTROLLED TRIAL

Comparing the histological assessment following ridge preservation using a composite bovine-derived xenograft versus an alloplast hydroxyapatite-sugar cross-linked collagen matrix

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Abstract

Background: This randomized controlled trial was designed to evaluate the histological wound healing and alveolar ridge dimensional changes following ridge preservation using two different xenograft/collagen matrices.

Methods: Fifty-four patients each with non-molar teeth that required extraction and replacement with dental implants were enrolled. Teeth extractions were completed with minimal flap reflection and were randomized to receive ridge preservation with either 90% bovine-derived xenograft granules in a 10% porcine collagen matrix (Group A) or a sponge-like matrix of 80% microparticulate hydroxyapatite alloplast graft with 20% sugar cross-linked porcine type 1 collagen (Group B). After 16 weeks of healing and at the time of implant placement, a bone core biopsy was harvested followed by dental implant placement. The primary histological outcome evaluated were percentage of vital bone formation and connective tissue/other (fibrous tissue and marrow space). Secondary outcomes included the change in alveolar ridge width and the buccal and lingual ridge height. Statistical analysis was completed with two-sample *t*-test and Fisher exact test.

Results: Forty-four patients completed the study, 23 in group A and 21 in group B. Group B presented with statistically significantly ($p = 0.02$) more percentage of vital bone (39.3 ± 17.8) than group A (26.8 ± 15.8). No statistically significant difference was observed for changes in alveolar ridge dimensions.

Conclusions: Group B, when used for ridge preservation, yields statistically significantly more vital bone over a 4-month healing period. Ridge dimension changes were similar between the two groups and were adequate for implant placement.

KEYWORDS
alveolar bone grafting, bone resorption, dental implants, tooth extraction, xenografts

1 | INTRODUCTION

Alveolar ridge preservation is performed to minimize dimensional changes of the alveolus following tooth extraction to aid in site development for ideal implant placement.[1] The effectiveness of this procedure has been confirmed by several studies including a systematic review and meta-analysis by Avila-Ortiz et al.[2] In this study it was determined that alveolar ridge preservation compared with tooth extraction alone, decreased horizontal (1.99 mm), vertical mid-buccal (1.72 mm), and vertical mid-lingual (1.16 mm) bone resorption. These findings were irrespective of the type of the particulate graft used for ridge preservation.

Various grafting materials have been recommended for ridge preservation, including allografts, xenografts, alloplasts, and autografts. Autogenous bone is considered the gold standard for bone grafting due to its osteogenic, osteoinductive, and osteoconductive properties, and the absence of immunologic reactions with its use.[3] The largest disadvantage with using autogenous bone for grafting is the morbidity associated with a second surgical site. This increases patient discomfort and surgical time.[4] For this reason, as well as other clinician motivated reasons, allografts, xenografts, and alloplasts have been chosen as substitutes for autogenous bone grafting. In this study, two xenograft/collagen matrices were compared and used for ridge preservation. The primary objective of this study was to evaluate if there is a difference in histologic wound healing following tooth extraction and ridge preservation between groups treated with either the 90% bovine-derived xenograft granules in a 10% porcine collagen matrix (Group A)[*] or the sponge-like matrix of 80% synthetic microparticulate hydroxyapatite alloplast graft with 20% sugar cross-linked porcine type 1 collagen (Group B).[†] The secondary outcomes assessed included the change in alveolar ridge width and the buccal and lingual ridge height.

The control product, Group A, consists of bovine-derived xenograft granules in a porcine collagen matrix and is a commonly used xenograft in dentistry. This xenograft/collagen matrix has been successfully used in many surgical procedures including ridge preservation[5] sinus augmentation,[6] and guided tissue regeneration.[7] The test product, Group B, is a sponge-like matrix of 80% synthetic microparticulate hydroxyapatite alloplast graft with 20% sugar cross-linked porcine type 1 collagen. To the authors' knowledge, this is the first human study that evaluated the test product for ridge preservation.

The proprietary technology used for collagen cross-linking of Group B includes non-enzymatic glycosylation of the collagen with non-toxic natural reducing sugars such as glucose, galactose, fructose, and ribose that cross-links the collagen forming the graft matrix. Two previous studies that evaluated the effectiveness this cross-linking technology with porcine type 1 collagen membranes reported histologic evidence of ossification directly on glycated collagen, with new bone formation at the junction of the membrane and underlying tissues.[8,9] It is believed that the ribose-based cross-linked collagen functions as a scaffold for direct ossification via the peptide sequence from osteopontin, collagen-binding motif (CBM). CBM binds to collagen and induces mineralization. These peptide sequences can be added to collagenous materials such as a regenerative membrane.[10] The value of this study lies in the histological evaluation of the effectiveness of the Group B proprietary technology in graft form for a surgical procedure common in practice, and its comparison with the well tested and highly used Group A product.[11–13]

The null hypotheses of this study are that there is no significant difference in the percentage of vital bone or CT/other tissues and in alveolar ridge dimensions between the two xenografts when used for ridge preservation.

2 | MATERIALS AND METHODS

2.1 | Patient enrollment

The experimental design of this parallel two-arm randomized prospective clinical trial was reviewed and approved by the Institutional Review Board of the University of Texas Health San Antonio (UTHSA), San Antonio, Texas (Protocol number HSC19-0455H) in agreement with the Helsinki Declaration of 1975, revised in 2013 and was registered as a clinical trial as NCT04338516. Power analysis determined 21 patients were needed for each group. Accounting for an anticipated 30% dropout rate, 27 patients were recruited for each group for a total of 54 patients. The primary source of patients recruited for the study was from the predoctoral and Periodontics Clinics at University of Texas Health Science Center School of Dentistry between November 2019 and February 2021. The inclusion criteria consisted of the following: (1) a non-molar tooth requiring extraction and planned for replacement with a dental implant, (2) adequate restorative space for a dental implant-retained restoration, (3) a minimum of 10 mm of alveolar bone height to allow for implant placement without impingement on adjacent vital structures, and (4) proper tooth root position to allow for a bone core harvest within the prior socket and at an ideal implant position. Patient exclusion criteria included: (1) pregnant women or

[*] BioOss Collagen, Geistlich Pharma North America, Princeton, NJ, U.S.A.
[†] Ossix Bone, Datum Dental, Lod, Israel.

planning to become pregnant during the study period, (2) currently smoking >10 cigarettes per day, (3) active infection other than periodontitis, (4) patients with a systemic disease or on medications that affect soft and hard tissue healing, and (5) patients not willing to cooperate with the study follow-up time period.

2.2 | Surgical protocol

All enrolled patients provided written informed consent before participating in the study. The surgeries were performed by periodontal residents supervised by board-certified periodontal faculty. This study is one of 14 similar studies done by this research group over the past several years.[14–27] Alginate impressions were taken of the arch that contained the study site, and a stone model was fabricated from the impression. A 1-mm thick clear thermoplastic acrylic stent[‡] was made of the surgical site and adjacent teeth for utilization during both surgeries for repeated clinical measurements of the alveolar ridge. One pre-extraction measurement was made, the width of keratinized tissue. The width of keratinized tissue was measured from the mid-buccal to the mid-lingual at the sites planned for extraction. Local anesthesia was administered, minimal flap reflection (approximately 3 mm apical to the alveolar crest) was performed, and a minimally traumatic extraction was done. The socket was evaluated for the presence of a fenestration or dehiscence following soft tissue debridement and copious irrigation with sterile saline. Final determination of enrollment into the study was done by verifying that a bony dehiscence >50% of the socket depth was not present. If a dehiscence greater than 50% was present, the patient was removed from the study. Randomization into either the 90% bovine-derived xenograft granules in a 10% porcine collagen matrix (Group A) or the sponge-like matrix of 80% micro-particulate hydroxyapatite alloplast graft with 20% sugar cross-linked porcine type 1 collagen (Group B) was completed by selecting an unlabeled and sealed envelope. The following postextraction measurements were taken: ridge width, buccal and lingual ridge height, buccal and lingual plate thickness, and the depth of the socket (Figure 1). Ridge width was measured 4 mm apical to the facial and lingual bony crests using a ridge caliper, through two small holes made in the flange of the stent (Figure 1). Ridge height was measured to the nearest 0.5 mm using a periodontal probe[§] through two holes made in the occlusal portion of the stent over the buccal and lingual bony crests. Ridge thickness was measured using an Iwanson gauge[**] 1 mm apical from the bony crests. The depth of the socket was measured from the base of the socket to the buccal and lingual alveolar crests to the nearest 0.5 mm. After all the clinical measurements were made, ridge preservation was performed using either group A or group B xenograft. Both xenografts were hydrated with the patient's own blood from the extraction socket. A membrane barrier was not used over the bone graft and no attempt was made to achieve primary closure. The flaps were replaced to their original position and sutured using 4-0 Polyglactin suture.[††]

Postoperative instructions were given to the patients verbally and in written form. Patients were prescribed an oral antibiotic regimen for 7 days consisting of either amoxicillin 500 mg three times a day, or clindamycin 300 mg three times a day if the patient had a penicillin allergy. Patients were advised to rinse with 15 ml of 0.12% chlorhexidine twice daily for 30 s each rinse for 2 weeks. Over-the-counter acetaminophen and ibuprofen were recommended for management of postoperative discomfort. Patients were seen for a postoperative appointment approximately 3 weeks (±1 week) after the procedure.

A cone-beam computed tomography (CBCT) scan was taken at 3 months (± 2 weeks) following the first surgery if requested by the surgeon for implant placement planning. The second surgery occurred ≈ 16 weeks after the first surgery. Following profound local anesthesia, ridge width was measured in the same manner as the first surgery using the stent and ridge calipers at the prospective implant site. A full thickness flap was then reflected, and the ridge height was measured at the same locations using the same technique performed in the first surgery. The coronal 8 mm of the implant osteotomy was prepared using a trephine drill with a 2 mm internal and 3 mm external diameter[‡‡] to obtain a bone core sample from the previously ridge preserved site. The bone core sample was stored in 10% neutral buffered formalin solution. The remaining apical portion of the osteotomy was prepared using the appropriate implant drills per the manufacturer's protocol. The surgeon was asked to record the tactile bone density at the site using the Lekholm and Zarb[28] classification as types 1, 2, 3, or 4. The inherent subjectivity associated with assigning a classification type was mitigated by a verification step performed by the calibrated supervising board certified faculty members and each surgeon being well versed in the classification system. Additional bone grafting was performed if implant thread exposure occurred, or a thin bony plate was present on the buccal or lingual

[‡] Clear Splint Biocryl 1mm/125mm Round, Great Lakes Orthodontic Labs, Tonawanda, NY, U.S.A.
[§] UNC-15 probe, G. Hartzell & Son, Concord, CA, U.S.A.
[**] Iwanson gauge, Henry Schein Dental, Melville, NY, U.S.A.
[††] Vicryl Ethicon, U.S.A.
[‡‡] Trephine bur, Salvin Dental Specialties, Charlotte, NC, U.S.A.

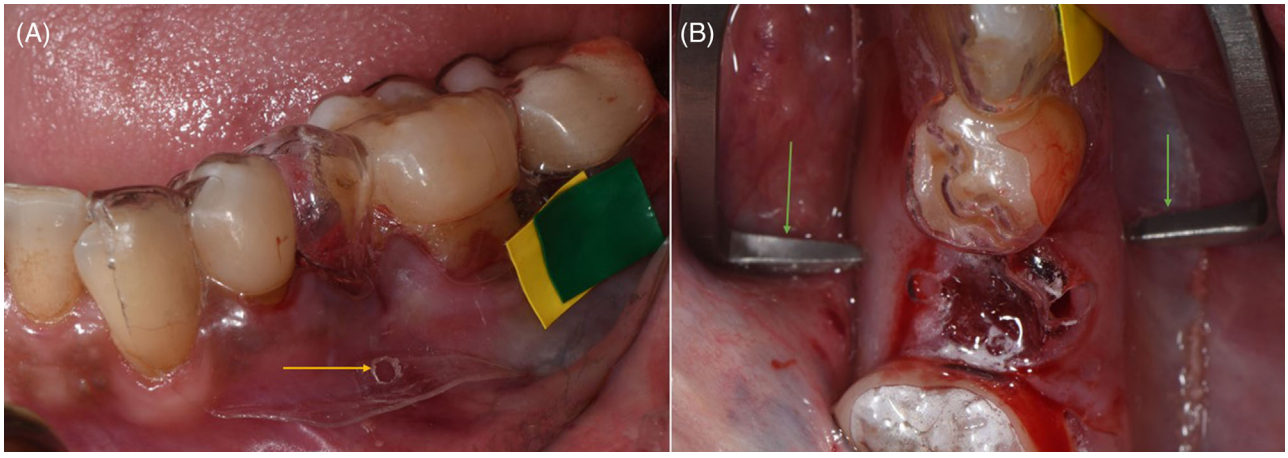


FIGURE 1 (**A**) Thermoplastic acrylic stent in please. Yellow arrow pointing out the hole at 4 mm apical to alveolar crest to allow for ridge width measurement with calipers. (**B**) Thermoplastic acrylic stent in place with calipers (green arrows) measuring the ridge width through a hole at 4 mm apical to alveolar crest

aspect of the implant. Study participation ended at the time of implant placement. A postoperative exam was done 10–14 days following the surgery, and the patient's healing was monitored until the implant was ready to be restored.

2.3 | Histologic processing and analysis

The histological processing steps and morphometric analysis for this study were identical to the previously established guidelines from the preceding studies in this research group.[14–27] The bone cores were removed from the trephine burs after being fixed in 10% neutral buffered formalin for a minimum of 72 h. The samples were submitted for processing in the same solution. The processing of the cores included several steps, with the initial step being decalcification of the core using hydrochloric acid (HCL) for up to 2 h. The samples were then placed in a tissue processor[§§] that progressively dehydrated the samples using sequential 1-h ethanol baths of 75%, 90%, and 100%, followed by a xylene bath and two paraffin baths. The samples were then embedded in paraffin wax using a paraffin embedder.[***] They were sectioned to a thickness of 4 um and placed on glass slides, with each sample providing seven to nine slices. The staining used was an acid fuchsin and a combination of eosin Y and orange G.[†††] The highest quality slice from the center of the core that was most representative of the bone core was selected for histomorphometric analysis. The analysis was performed by one single examiner blinded to the bone core group allocation. With the use of a microscope, each slice was examined at 4× magnification.[‡‡‡] A series of overlapping JPEG images were captured and imported into an image processing software.[§§§] The images were then merged to form one continuous image of each bone core, to allow for identification and outlining of the different tissue types. For group A, vital bone, residual graft, and CT/other were outlined and analyzed. Due to the nature of the group B product, only vital bone and CT/ other were identified for analysis. Vital bone tissue was identified by the presence of osteocytes within the mineralized tissue, residual graft was noted by the absence of osteocytes in mineralized tissue, and the remaining tissues were categorized as CT/other. Each of the traced tissue types were saved as JPEG images and changed to binary (black and white) images using the image analysis software.[****] These converted images were then used to calculate the total number of pixels in each image. The percentage of each different tissue type was determined by calculating the total number of pixels in each tissue component divided by the total number of pixels in all the tissue components combined.

2.4 | Statistical analyses

Sample size estimation for adequate power was based on the effect sizes that were reported in a previous study for ridge preservation, which used similar methodologies for assessment by this research group.[15] Considering an impactful difference of at least 10% in vital bone between the groups as relevant, it was estimated that the optimal

[§§] Tissue-Tek VIP 1000, Sakura Finetek USA, Torrance, CA, U.S.A.
[***] Leica RM2155 automated microtome, Leica Microsystems, Buffalo Grove, IL, U.S.A.
[†††] Treosin, Statlab Medical Products, Lewisville, TX, U.S.A.
[‡‡‡] Vano AH-2, Olympus America, Center Valley, PA, U.S.A.
[§§§] Adobe Photoshop CC, Adobe, San Jose, CA, U.S.A.
[****] Image J, National Institutes of Health, Bethesda, MD, U.S.A.

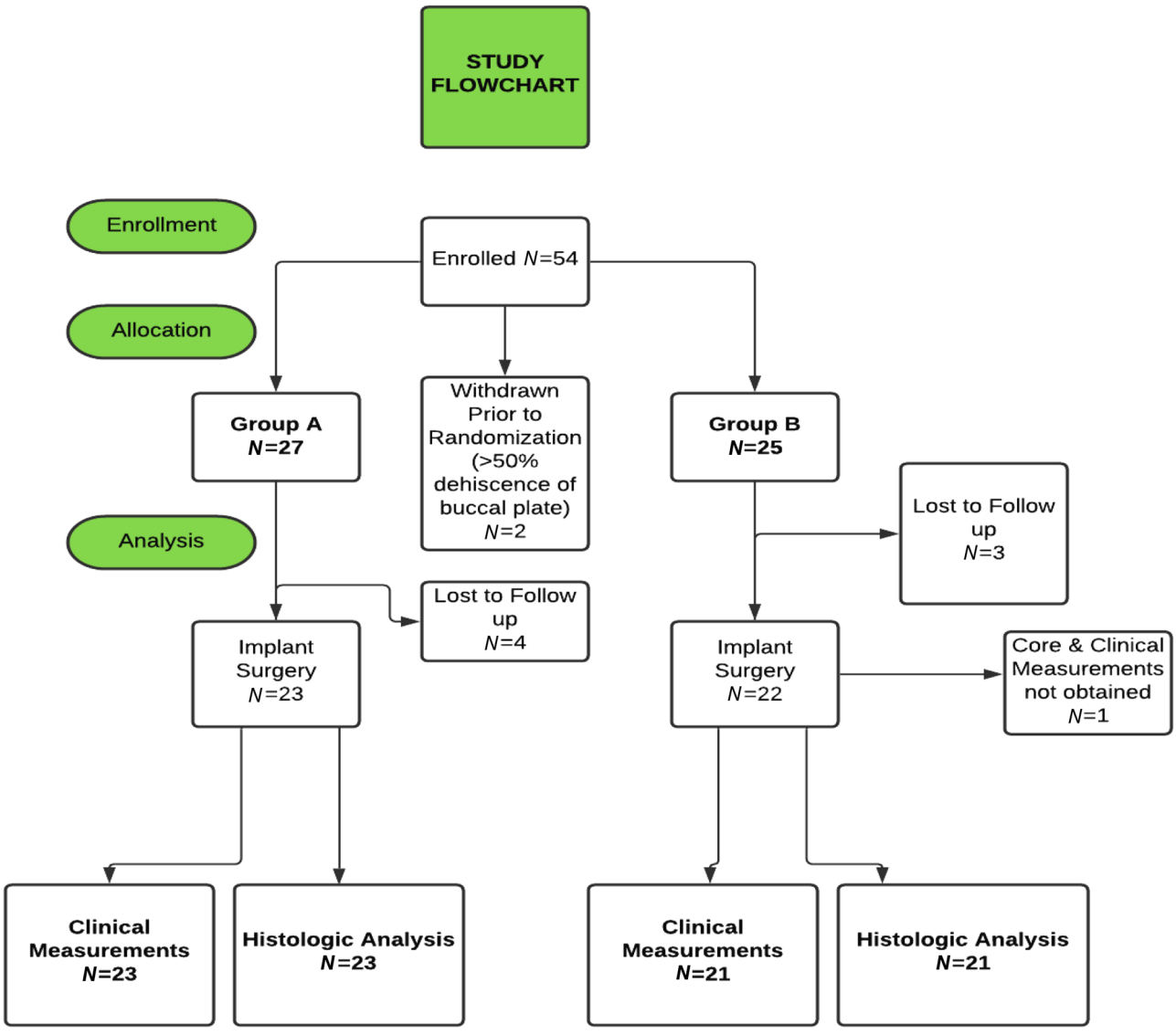


FIGURE 2 CONSORT diagram presenting study outline

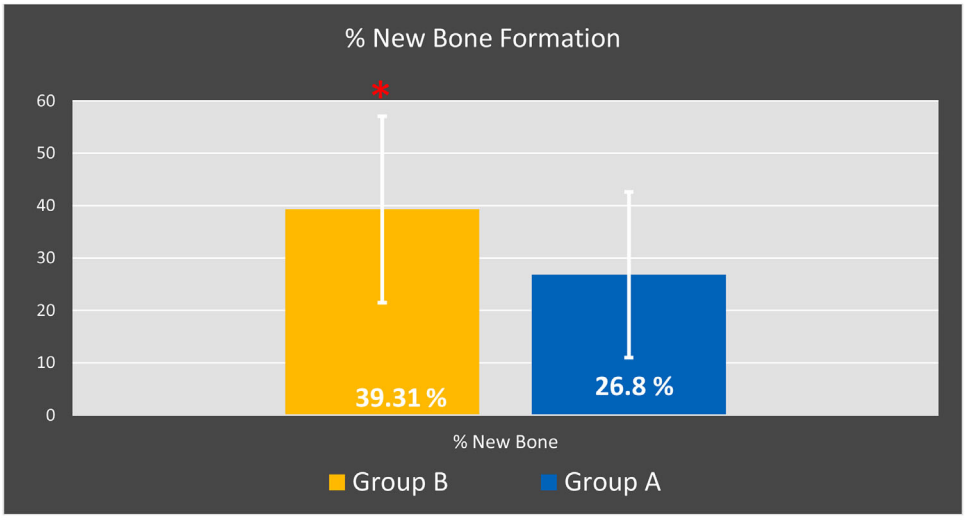
sample size to yield 80% power was 21 patients per arm using a two-sided *t*-test and alpha = 0.05.

Two-sample *t*-tests were used to evaluate intergroup differences for continuous outcomes, while categorical variables (i.e., sex, tooth site location, need for additional GBR "yes/no") were assessed using Fisher exact tests at a significance level alpha = 0.05. Results were summarized and presented as means ± SDs.

3 | RESULTS

Fifty-four patients were enrolled in the study, 26 females and 28 males, with an average age of 55 years (see Figure S1 in online *Journal of Periodontology*). Forty-four patients completed the study (Figure 2). No postoperative infections or complications occurred following the surgeries. During the duration of the study no subject suffered any adverse event due to the materials tested or the procedures.

Forty-four bone core samples were harvested (23 from group A, 21 from group B). One bone core sample from group B could not be harvested due to complete fibrous encapsulation of the graft material evident at the time of implant placement. Primary implant stability was achieved for all implants placed; however, there was a statistically significant ($p = 0.0005$) difference found between the groups for implant insertion torque, with a higher insertion torque noted in group A. The implant insertion torque range was between 20 and 40 NCM for group A and 5–35 NCM for group B. Eleven patients required additional bone grafting at the time of implant placement (six from group A group and five from group B) because of a thin buccal plate.



* Statistically significant ($p<0.05$); $p=0.02$

FIGURE 3 Graphic representation of percent new vital bone formation, connective tissue/other and residual graft. Group B presented no residual graft particles

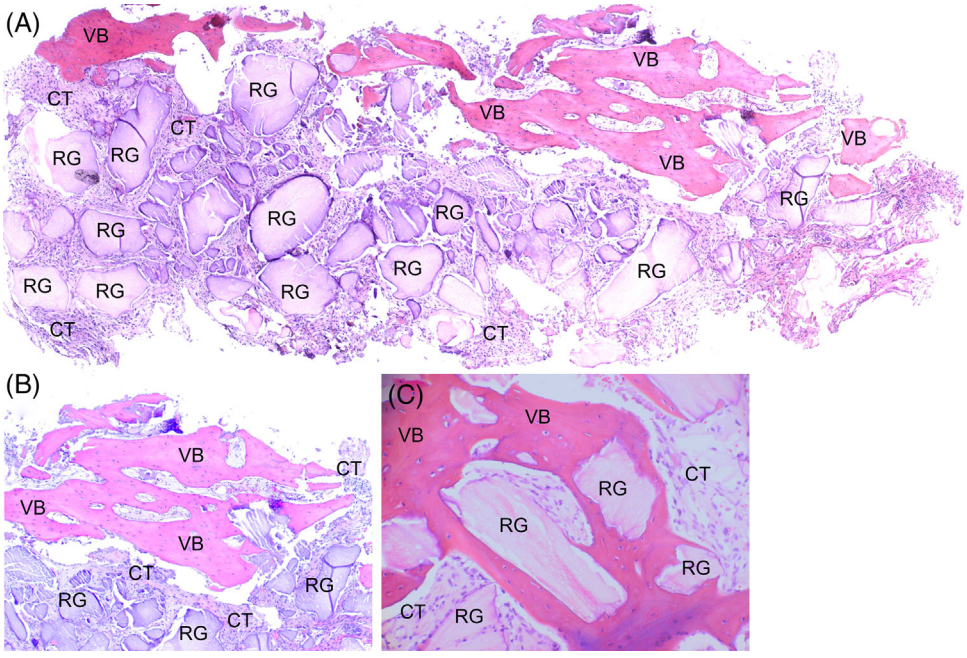


FIGURE 4 (**A**) Group A core in its entirety at 4× magnification. (**B**) Section of the same core at 4× magnification. (**C**) Section of the same core at 10× magnification. VB, vital bone identified by the presence of osteocytes; RG, residual graft particles; CT, connective tissue/other

The primary histologic outcomes of the study can be found in Figures 3–5. There was a statistically significant difference in vital bone formation between the two groups (group A = 26.8%, group B = 39.3%; p-value = 0.02), providing a 12.5% greater absolute mean vital bone formation in group B. No statistically significant difference was noted for percentage of CT/other between the two groups. Only the percentage of new vital bone and CT/other were able to be analyzed in this study because no residual graft particles were found in the Group B samples at 4 months of healing. It is speculated that the lack of residual graft particles may be due to the fact that the bone cores were harvested at one point in time which does not allow histological evaluation of earlier healing time points when residual graft particles may have been detected in Group B. Additionally, the hydroxyapatite found within the xenograft/collagen matrix of the Group B product is non-sintered in a microparticulate form which likely

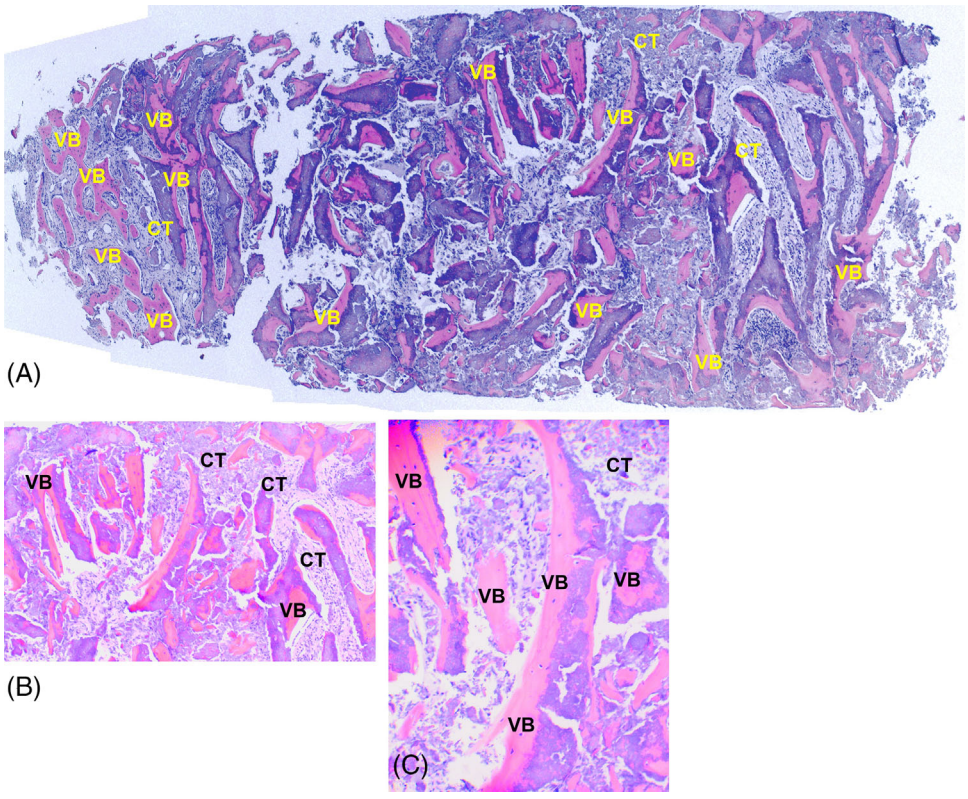


FIGURE 5 (**A**) Group B core in its entirety at 4× magnification. (**B**) Section of the same core at 4× magnification. (**C**) Section of the same core at 10× magnification. VB, vital bone identified by the presence of osteocytes; CT, connective tissue/other

resorbed during the remodeling/ossification process. During the initial steps of histologic processing, the bone cores were demineralized with HCL acid which could have possibly decalcified any residual graft particles present, leaving only residual collagen. Detecting a histologic difference between the residual collagen from the graft and the newly formed CT would not have been possible so it was all analyzed as one tissue group (CT/other). Vital bone tissue was identified by the presence of osteocytes within the mineralized tissue and the remaining tissues were categorized as CT/other. As shown clearly in Figure 5, new vital bone is forming around and within the CT/other tissues in Group B. This may be due to the amount of collagen present in each of the bone products, with Group B having twice as much collagen. Additionally, based on the histological evaluation of the bone core samples it is speculated that Group B bone graft heals more like native bone (resorption of the bone graft followed by deposition of new bone) which resulted in no residual graft particles. Conversely, Group A bone graft appears to heal by apposition of new bone around the residual graft particles followed by resorption and presented with ≈ 18% residual graft particles. As shown clearly in Figure 4, new vital bone is forming around the residual graft particles remaining in Group A. At the 4-month time point when the implants were placed, the presence of remaining graft particles in Group A, as is almost always seen when performing ridge preservation with xenografts or allografts,[14–25] may be responsible for the lower percentage of new bone compared with Group B. Because this study examined only a single healing time point, it is unknown if more vital bone might form in both groups over longer time periods.

The findings for ridge dimensional changes are provided in Table 1. The mean baseline ridge width for group A was 11.7 mm (SD = 1.6), and for group B was 10.4 (SD = 2.3), with this difference being significant (p = 0.03). However, no statistically significant difference was found for the change in ridge width between the two groups after 16 weeks of healing. The mean buccal plate thickness of group A was 1.0 mm (SD = 0.6), and for group B was 0.9 mm (SD = 0.6). Group A had a mean loss in lingual ridge height of −0.9 mm (SD = 1.3) and −0.7 mm (SD = 1.7) on the buccal aspect. The mean change in lingual ridge height for group B was −1.1 mm (SD = 1.6) and for the buccal ridge height was −0.2 mm (SD = 1.6) (Table 1). In summation, a slightly greater mean loss in lingual ridge height was evident in group B and a greater mean loss in buccal ridge height was found in group A. These differences in the change in ridge height were not statistically significant.

TABLE 1 Ridge dimensional changes

Variables		Group A	Group B	*p*
Baseline ridge width (mm)	Mean (SD)	11.7 (1.6)	10.4 (2.3)	0.03*
Initial buccal plate thickness (mm)	Mean (SD)	1.0 (0.6)	0.9 (0.6)	0.84
Change in lingual ridge height (mm)	Mean (SD)	−0.9 (1.3)	−1.1 (1.6)	0.83
Change in buccal ridge height (mm)	Mean (SD)	−0.7 (1.7)	−0.2 (1.6)	0.33
Change in ridge width 4 mm apical from crest (mm)	Mean (SD)	−0.9 (1.7)	−1.8 (1.9)	0.11

*Statistically significant ($p < 0.05$).

4 | DISCUSSION

The focus of this study was to evaluate the histologic wound healing and clinical outcomes of ridge preservation using two different xenograft/collagen matrices.

The primary outcome of this study was to histologically evaluate the percentage of vital bone formation and CT/other (fibrous tissue and marrow space) following 4 months of healing at a previous tooth extraction site that received ridge preservation and is summarized in Figure S2 in the online *Journal of Periodontology*. This outcome is indicative of wound healing at the site. The percentage of vital bone formation shows the amount of new bone formed following ridge preservation, with a higher percentage equating to better healing of the site. The percentage of CT/other is the amount of tissue that is neither native bone or residual graft material, and that may include CT or a marrow space. In this study, a statistically significant difference in percentage of vital bone formation was found between the groups, with group B having a higher percentage (see Figure S2 in the online *Journal of Periodontology* and Figure 3). The results from this study differ from another study performed by this same research group that followed similar methodologies and assessed the same study outcomes. Cook et al. compared the Group A product used in our study to a xenograft sponge composed of 70% cross-linked type I bovine collagen coated with a layer of non-sintered hydroxyapatite material. A statistically significant difference was found for percentage of vital bone between the two groups (32.83% for the Group A product and 47% for the other xenograft). The differences in results between our study and the Cook study may be attributed to a longer healing time (total of 21 weeks of healing time) and the use of a barrier membrane.

The secondary outcome of this study evaluated ridge dimensional changes after ≈ 16 weeks of healing (Table 1). No statistically significant difference was found for the change in ridge width or ridge height between the two groups. At the time of implant placement, the tactile bone density of the grafted sites was low in both groups. In one of the group B subjects, a bone core could not be obtained due to the presence of only granulation tissue at the site. This tissue could not be harvested for analysis due to its extreme fragility. Despite the low tactile bone density of the study sites, all 44 implants (23 in group A, 21 in group B) placed attained primary stability. However, a statistically significant ($p = 0.0005$) difference was found between the groups for implant insertion torque, with a higher insertion torque noted in group A. The implant insertion torque range was between 20–40 NCM for group A and 5–35 NCM for group B. Due to the low tactile bone density of the grafts, a cover screw was placed for all implants, with a second stage surgery performed after 4 months of healing. While the study ended at the time of bone core harvest, re-entry of the study sites allowed for additional clinical observations of healing. Although no significance can be tied to these observations, they are interesting points to note that may affect some clinicians' practice. By 8 months of healing the group B sites had a radiographic appearance very similar to healed native bone, which is contrary to the radiolucent appearance seen at 4 months of healing when immature vital bone predominated. This likely indicates further maturation and calcification of newly forming bone in Group B over time. At stage two implant surgery, most of the group B sites had bone formation over the implant cover screws requiring removal, which may indicate continued ossification of the graft. The healing time for three subjects (two from group A, one from group B) was extended by a month and a half due to the COVID clinic closure. At the time of bone core harvest and implant placement, these sites had healed for ≈ 5.5 months. The tactile bone density at these sites was far denser than all the other study sites. This finding indicates that a longer healing time is beneficial when using xenografts for ridge preservations.

Previous studies completed by this group investigated the healing potential of allograft materials in the same ridge preservation model.[15–22,24–27] Studies that investigated the short (8–10 weeks) versus long (18–20 weeks) healing time with different allografts found that an increased amount of vital bone was seen in the long-term groups similar to the percentage of vital bone found in this study. Specifically, Borg et al., 2015 at the 18–20-week healing time point, reported 36% vital bone with a graft material of 70% freeze dried bone allograft (FDBA) and

30% demineralized FDBA. In the same study and at the same time point of 18–20 weeks, FDBA alone was reported to result in 24% vital bone.[16] Similarly, Wood et al., 2012 report 24% vital bone formation at 18–20 weeks when using FDBA alone.[27] It is of great significance that Group B in the current study resulted in 39% new vital bone at only 14–16-week healing time point. It is safe to assume that the percentage of new vital bone formation would increase with increased healing time for both groups A and B.

Further research is needed to assess the results of both materials tested after a longer healing period as well as with those used when a barrier membrane is used, both of which are considered limitations of this study.

5 | CONCLUSIONS

The findings of this study reveal that there was significantly greater vital bone formation in Group B within and around the CT/other tissue with no residual graft particles present. Group A presented ≈ 18% residual particles surrounded by new vital bone and CT/other tissue. No statistically significant difference was noted for percentage CT/other between the two groups. The two xenografts tested allowed all patients enrolled in the study to receive an implant.

ACKNOWLEDGMENTS

This study received financial support from Datum Dental, Bat Sheva, Lod, Israel and donation of graft, membrane, and suture materials. The study was registered at the Institutional Review Board of the University of Texas Health San Antonio (UTHSA), San Antonio, Texas (protocol number HSC19-0455H) and the National Clinical Trials Database (number NCT04338516). Drs. Casarez-Quintana, Palaiologou, Mealey, and Kotsakis report no conflicts of interest regarding this study.

AUTHOR CONTRIBUTIONS

Drs. Casarez-Quintana, Mealey, and Palaiologou each contributed to conception, design, data acquisition, and interpretation, and drafting and revising the manuscript. Dr. Kotsakis contributed to data analysis and interpretation and to drafting and revising the manuscript. All authors have given their final approval of the version to be published.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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