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HUMAN RANDOMIZED CONTROLLED TRIAL

A randomized controlled trial on the impact of healing time on wound healing following ridge preservation using a 70%/30% combination of mineralized and demineralized freeze-dried bone allograft

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Abstract

Background: To compare the histologic difference in healing between ridge preservation sites treated with a combination allograft of 70% mineralized and 30% demineralized freeze-dried bone allograft (FDBA) evaluated at 8 to 10 weeks versus 18 to 20 weeks post-extraction. Changes in morphological ridge dimensions were also evaluated.

Methods: Forty-four patients with a single-rooted tooth to be extracted and replaced by a dental implant were recruited for this study. At time of extraction, measurements were taken with a custom acrylic stent, and the extraction socket was grafted with the combination allograft and covered with a nonresorbable membrane. Patients were randomly assigned to the short-term (8 to 10 weeks) or long-term (18 to 20 weeks) healing group. Sites were re-entered for study measurements, a bone core sample, and implant placement. Bone cores obtained during implant placement were analyzed histologically to determine percentages of vital bone, residual graft, and CT/other.

Results: Thirty-eight of the 44 patients completed the study, 19 in each group. There was a significant difference between the two groups for mean percent vital bone formation (short-term = 18.17%, long-term = 40.32%, $P = < 0.0001$) and percentage of residual graft (short-term = 41.54%, long-term = 23.59%, $P = < 0.0001$). There was no difference in morphological changes between the two groups.

Conclusion: Ridge preservation using combination FDBA resulted in approximately twice as much vital bone and half as much residual graft material after 18 to 20 weeks of healing compared to only 8 to 10 weeks healing.

KEYWORDS

alveolar bone grafting, alveolar bone loss, bone resorption, bone transplantation, dental implants, tooth extraction

1 | INTRODUCTION

As dental implants have become a primary means of replacing hopeless teeth, predictably maintaining the alveolar bone dimensions for future implant placement is a topic of interest for dental clinicians. If extraction sites are allowed to heal naturally, considerable remodeling occurs, which can complicate implant placement post-healing.[1,2] A systematic review

by Avila-Ortiz et al.[3] clearly showed that ridge preservation of extraction sockets with particulate graft (autogenous, allograft, or xenograft) decreased the amount of dimensional changes compared with sites not grafted. Aside from maintaining the alveolar bone dimensions, another important consideration is the quantity and quality of vital bone formation that will ultimately surround the future dental implant.[3] A recent study[4] found that there was a higher mean percent vital bone when no grafting was completed and that no one bone substitute was superior to another, but considerable loss of ridge height and width accompanies a non-grafted extraction socket.[1–3,5,6] A goal of ridge preservation is to maintain the overall size and shape of the ridge while also allowing formation of new vital bone. Although autogenous grafts possess all beneficial qualities of the ideal bone graft, they are associated with relatively high morbidity[5] and increased surgical time, and they lack evidence demonstrating their superior qualities over other options.[4] Bone particulate allograft is a commonly used material to predictably maintain alveolar ridge dimensions[7] while also providing a scaffold for new host bone formation.[8]

Mineralized (FDBA) and demineralized freeze-dried bone (DFDBA) are two major types of bone allograft materials used in the surgical realm of dentistry. The processing of FDBA and DFDBA is virtually identical with the exception of the demineralization step, unique to DFDBA. This step allows bone morphogenic proteins in DFDBA to be utilized immediately upon being placed in an extraction site.[8,9] FDBA, on the other hand, will undergo this demineralization process in vivo, when osteoclasts release osteoinductive proteins which are trapped in mineralized particles.[10] DFDBA is both osteoconductive and osteoinductive, is radiolucent, has a smaller granule size when compared to FDBA, and only utilizes cortical bone as its source.[9] Conversely, FDBA is osteoconductive by nature, is radiopaque, has a larger granule size which may provide a better scaffold, and may continue to release beneficial osteoinductive proteins as it is turned over in situ.[8,11] Wood and Mealey[11] found a quantitative difference between DFDBA and FDBA with respect to mean percent of vital bone (38.4% and 24.6%) and residual graft (8.9% and 25.4%), respectively after 5 months of healing following ridge preservation. The combination of FDBA and DFDBA into a single allograft may provide an ideal combination of properties from the mineralized and demineralized components.

Two influential studies laid the groundwork for the current study. Whetman and Mealey[12] examined wound healing in ridge preservation using 100% DFDBA at sites that were allowed to heal either 8 to 10 weeks or 18 to 20 weeks post-extraction. The long-term healing group had a significantly greater amount of vital bone formation and less residual graft than the short-term healing group. Borg and Mealey[13] compared the 70%/30% (FDBA/DFDBA) combination allograft against 100% FDBA and found 36.2% and 24.7% vital bone, respectively, at 18 to 20 weeks post-ridge preservation. The current study is the first study to evaluate wound healing after ridge preservation with the 70%/30% combination allograft at two commonly used timepoints for implant placement: 8 to 10 weeks and 18 to 20 weeks after tooth extraction. The primary objective of this parallel two-arm, randomized, controlled study is to determine histologically if there is a difference in the three principal tissues: vital bone, residual graft, and connective tissue/other between the 8 to 10 week and 18 to 20 week time points. Secondary outcomes include dimensional changes in ridge height and width in the short-term study group compared to the long-term group.

2 | MATERIALS AND METHODS

2.1 | Participant enrollment

The Institutional Review Board of UT Health San Antonio (UTHSA) approved this study, which was carried out in accordance with the Helsinki Declaration of 1975, revised in 2013. Standard deviations from previous studies by the authors' research group have ranged between 12.0% and 22.4% for mean percent new vital bone.[12,13] Power analysis determined that in order to detect a mean difference of vital bone formation of at least 1 SD or greater by Mann-Whitney *U* test at 5% level of significance and a power of 0.85, a sample size of 14 bone core samples per group was deemed necessary. Anticipating a potential 30% dropout rate, between November 2017 and August 2018, a total of 44 patients were recruited from the UTHSA School of Dentistry Graduate Periodontics Clinic, 22 in each group. Various inclusion criteria, adopted from similar studies[11–18] of the authors' research group, were required to be enrolled in the study: (1) one single-rooted tooth requiring an extraction and replacement with a dental implant, (2) minimum of 10 mm of vertical bone without interfering with adjacent vital structures, and (3) adequate restorative space for a dental implant restoration. Teeth to be extracted had to be in the same "restorative position" as the implant that would replace it. That is, the tooth root was also required to be in an ideal three-dimensional position to mimic future implant placement and to help ensure that the bone core, harvested at time of implant placement, did not incorporate native alveolar bone. Individuals were excluded if any of the following conditions were noted: (1) heavy smokers (≥10 cigarettes/d), (2) patients who were pregnant or had plans to become pregnant during the study period, (3) those unwilling or unable to commit to specific follow-up visits, or (4) presence of conditions or use of medications that might affect soft or hard tissue wound healing such as poorly controlled diabetes or use of steroids, antiresorptive agents, or immunosuppressant drugs.

2.2 | Surgical protocol

Written consent was obtained from all patients. A 1.0 mm thick clear thermoplastic acrylic stent* was made off a stone model from an alginate impression taken for each patient at the time of screening. Stents were trimmed and sterilized to allow for accurate and repeated measurements throughout the study period.

After profound anesthesia was attained, full-thickness flaps were reflected ≈3 mm apical to the alveolar crest to allow the overlying membrane to cover the bony crest. A minimally traumatic extraction was performed using either periotomes, piezosurgical extraction tips, and/or forceps, followed by soft tissue curettage of the alveolar socket and copious irrigation with sterile saline. To confirm inclusion criteria were met, the socket was inspected for dehiscences and fenestrations. If a buccal dehiscence was present and measured ≥50% of the total socket depth, that patient was exited from the study. A periodontal probe† was used to take all measurements. Socket depth was recorded to the nearest 0.5 mm from the base of the socket to the buccal and lingual aspects of the alveolar crest. Two holes were placed on the occlusal aspect of the stent over the buccal and palatal/lingual aspects of the tooth extracted to measure the distance from the stent to the buccal and palatal/lingual alveolar crest. Measurements were rounded to the nearest 0.5 mm. Two additional holes were made, one on the buccal and one on the palatal/lingual flange ≈4 mm apical to the alveolar crest. Ridge width was measured in these flange holes using Castroviejo ridge calipers‡ and also rounded to the nearest 0.5 mm. Thickness of the buccal plate was determined to the nearest 0.1 mm with an Iwanson gauge§, which was placed ≈1.0 mm apical to the buccal alveolar crest.

A non-resorbable, dense polytetrafluoroethylene (d-PTFE) barrier membrane¶ was trimmed, according to manufacturer's recommendations. The 70%/30% combination mineralized/demineralized FDBA# was hydrated with sterile saline and placed in the alveolar socket incrementally, as to prevent voids. The bone graft was placed up to, but not exceeding the height of the alveolar crest on the mesial and distal aspects of the extraction socket. The membrane was positioned to completely cover the graft, extending 3 mm apical to the bony crest. All of the allograft material was sourced from a single donor, an 18-year old male with an osteoinductivity score of 2 and 3 on a 4-point scale in the demineralized portion of the allograft. Primary closure was not attempted, and buccal and lingual/palatal flaps were reapproximated with 4-0 d-PTFE sutures.‖ Only after study measurements and grafting of the alveolar socket were completed, was the patient then randomly assigned to either the study group (8 to 10 week) or the control group (18 to 20 week) by opening a sealed envelope.

Postoperatively, patients were placed on amoxicillin 500 mg orally three times per day for 1 week. In the event the patient had a penicillin allergy, clindamycin 300 mg orally three times per day for 1 week was prescribed. An oral rinse of 0.12% chlorhexidine gluconate was prescribed to patients with instructions to rinse twice daily for 15 to 30 seconds. Post-operative follow-up visits were scheduled 7 to 10 days and 1-month post-extraction. The d-PTFE¶ membrane was removed at the 1-month appointment and a cone beam CT was taken ≈1 month prior to implant placement to aid the surgeon in appropriate bone core harvesting and implant osteotomy preparation.

Patients returned either at 8 to 10 weeks or 18 to 20 weeks post-extraction to have a bone core harvested and an implant placed at the site of ridge preservation. Following administration of local anesthetic and full-thickness flap reflection, measurements were taken with the same custom stent used at time of extraction. A bone core biopsy was taken with a hollow trephine drill.** The drill diameter measured 2 mm internally and 3 mm externally. Bone core samples measured ≈8 mm in length and once obtained, were placed into a 10% neutral buffered formalin solution. After procurement of the bone core sample, the study was deemed complete and an implant was placed, following the manufacturer's drilling protocols. If at the time of implant placement, thin bone or exposed implant surface was noted, guided bone regeneration was accomplished. Patients were seen for normal post-operative recall visits and then referred back to their restorative dentist for the final implant restoration, usually 3 to 5 months after implant placement.

2.3 | Histomorphometric analysis

The preparation of bone cores to be viewed histologically and the process by which images were traced and analyzed to yield a quantitative unit of measure have both been used in similar studies.[11–18] Bone core samples were processed by treating them with a decalcifying solution†† not exceeding 1 hour, depending on size of the specimen. This was followed by dehydration via a tissue processor‡‡ to which increasing

* Clear Splint Biocryl 1mm/125 mm Round, Great Lakes Orthodontic Labs, Tonawanda, NY.

† UNC-15 Probe, G. Hartzell & Son, Concord, CA.

‡ Castroviejo ridge calipers, Salvin Dental Specialties, Charlotte, NC.

§ Iwanson gauge, Salvin Dental Specialties, Charlotte, NC.

¶ Cytoplast PTFE TXT-200 singles, Osteogenics Biomedical, Lubbock, TX.

70%/30% Combination FDBA/DFDBA, Osteogenics Biomedical, Lubbock, TX.

‖ Cytoplast PTFE 4-0 sutures, Osteogenics Biomedical, Lubbock, TX.

** Trephine bur, Salvin Dental Specialties, Charlotte, NC.

†† Surgipath Decalcifier II, Leica Biosystems Inc., Buffalo Grove, IL.

‡‡ Tissue-Tek VIP 1000, Sakura Finetek USA Inc., Torrance, CA.

concentrations of alcohol (75%, 90%, and 100%) were gradually added to dehydrate the specimen, for a total of 3 hours. Two xylene baths were then used as clearing agents to replace the alcohol and prepare the specimen. Next, specimens were impregnated in paraffin via an embedder*. These solid specimens were then sliced to a thickness of 4 microns and were subsequently placed on glass slides. All of the bone core specimens were stained with Harris hematoxylin followed by a counterstain with a combination of eosin-Y, orange-G, and acid fuchsin†. The histomorphometric analysis was carried out using similar methodology from this same research group.[11–18]

Slices of 4 μm thickness were analyzed under a microscope at 1× magnification to help identify the best, most representative, section from each specimen. Sections were further analyzed at 4× magnification‡ and overlapping images were taken§. Depending on the size of the specimen, between six and 12 images were joined together using software¶ with a "photomerge" feature. A single image was then created, representative of the entire bone core sample.

These images were further examined using the microscope at minimum 20× magnification, and at times, 40× magnification to aid in tracing the three distinct tissue types: vital bone, residual graft, and connective tissue/other. A blinded examiner (AN), completed the histologic analysis of the bone core specimens (Figures 1 and 2). Residual bone graft particles were defined as mature lamellar bone, but with empty lacunae; in contrast, vital bone was identified as more woven in nature and always containing osteocytes present within the lacunae. CT/other was defined as anything other than bone, which included: fibrous tissue, blood vessels, and small voids or space within the specimen. After the three tissue types were traced and layered§, another imaging software# was utilized to convert these individual tissue layers to binary (black and white) images. The total number of pixels per tissue type, divided by the total area occupied by the specimen yielded a total area percentage for vital bone, residual graft, and CT/other.

2.4 | Statistical analysis

Means, standard deviations, frequencies and percentages were calculated for descriptive statistics. The two treatment groups, as well as other pairs of groups, were compared with *t* tests and verified with the non-parametric Wilcoxon test to assure the assumptions for the *t* test did not alter the results. Frequencies were compared with the exact χ^2 test. Relationships of two variables were studied with the Pearson correlation coefficient and verified again with the non-parametric

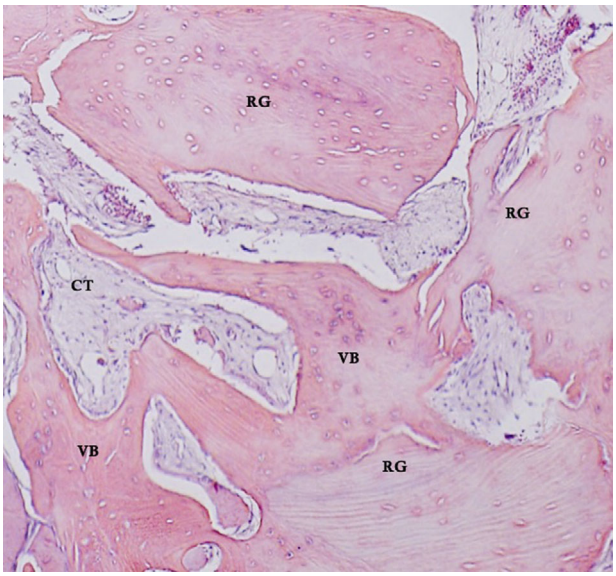

FIGURE 1 Representative samples of the 3 tissue types from a sample in the 8 to 10 weeks healing group. CT, connective tissue/other; RG, residual graft; VB, vital bone; (Harris hematoxylin and counterstain with combination of eosin-Y, orange-G and acid fuchsin; original magnification ×4)

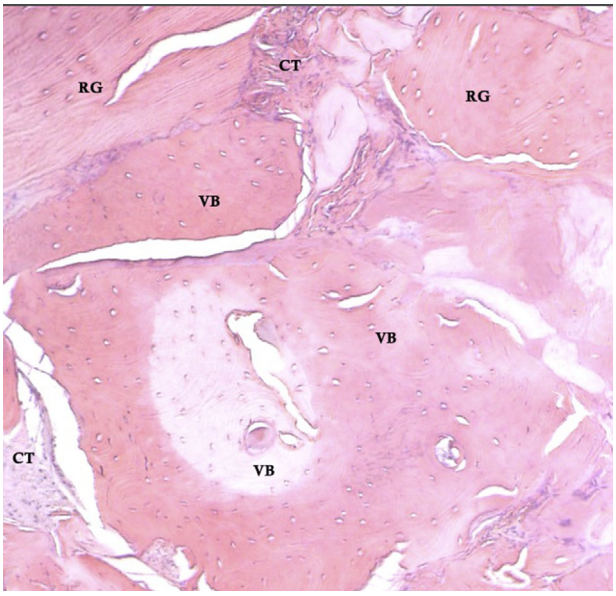

FIGURE 2 Representative samples of the 3 tissue types from a sample in the 18 to 20 weeks healing group. CT, connective tissue/other; RG, residual graft; VB, vital bone (Harris hematoxylin and counterstain with combination of eosin-Y, orange-G, and acid fuchsin; original magnification ×4)

* Leica RM2155 automated microtome, Leica Microsystems Inc, Buffalo Grove, IL.

† Treosin, Statlab Medical Products, Lewisville, TX.

‡ Vano AH-2, Olympus America, Center Valley, PA.

§ CellSens Version 1.4 Software, Waltham, MA.

¶ Adobe Photoshop CC, Adobe, San Jose, CA.

Image J, National Institutes of Health, Bethesda, MD.

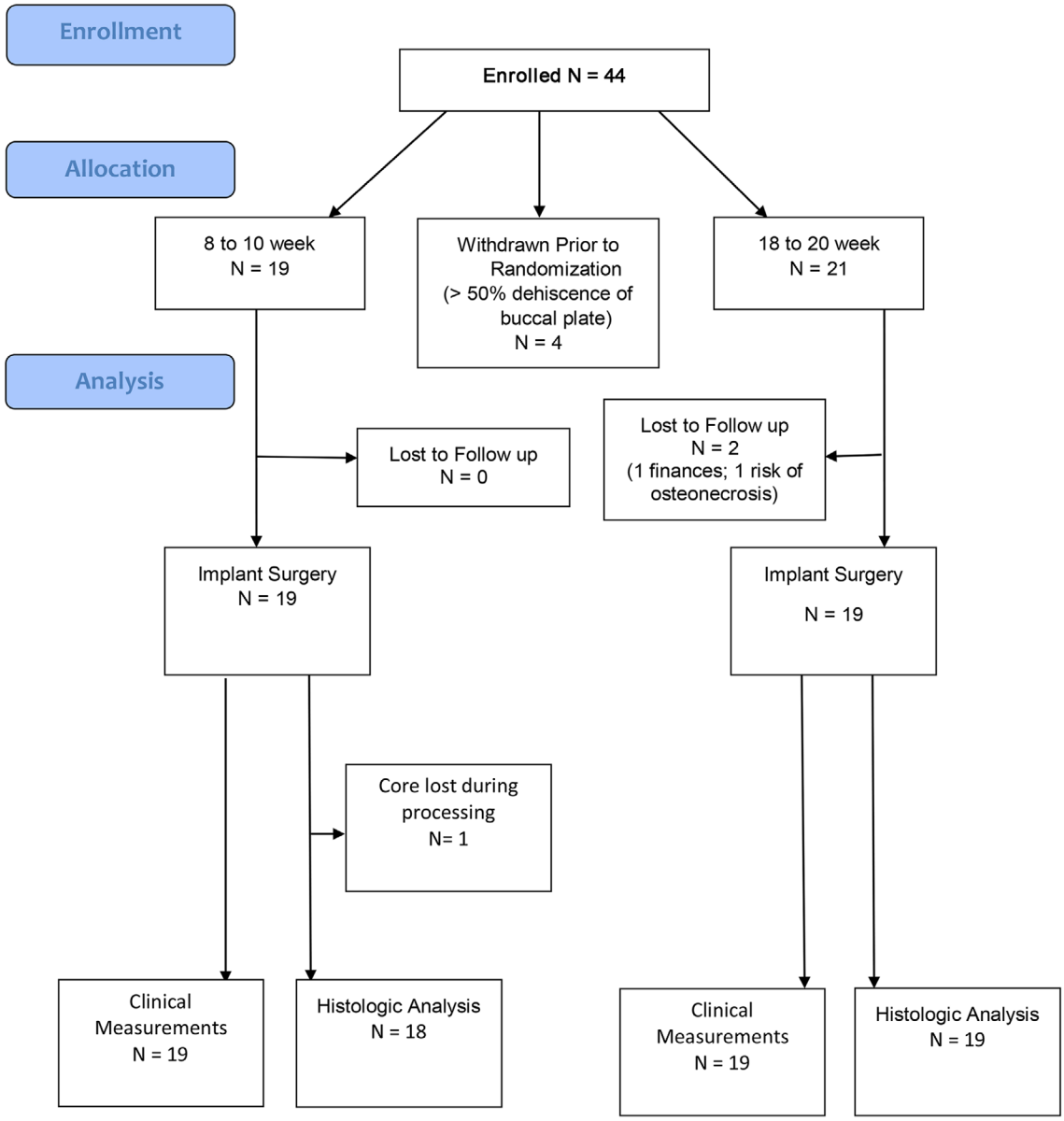

FIGURE 3 CONSORT flow diagram[20]

Spearman correlation. Statistical analysis software was used for all analyses.*

3 | RESULTS

Forty-four patients were enrolled in the study, 14 males and 30 females, with an average age of 59 (age range 32-86) (Figure 3). In total, six patients were exited from the study. Four patients had a dehiscence present at time of extraction which was ≥50% of the total socket depth, and hence did not meet inclusion criteria. One patient was unable to complete the study because of financial hardship. One additional patient was exited from the study because of post-operative complications at a different surgical site. No measurements were taken on patients who were exited from the study. There were four active smokers (<10 cigarettes/d) who participated in the study, two in each group. Three patients had well-controlled diabetes (HbA1c 6.5% to 7.2%), two in the 8 to 10 week group, and one in the 18 to 20 week group.

Bone cores were obtained from 38 patients (12 males and 26 females, with a mean age of 59) at time of implant placement and all 38 patients received dental implants. Additional grafting was performed in four patients in the short-term group and two patients in the long-term group. In total, 19 bone core samples were analyzed histologically from the 18 to 20 weeks group and 18 samples from the 8 to 10 week group. One bone core was lost because of processing.

* SAS Version 9.4 for Windows, SAS Institute, Cary, NC

TABLE 1 Primary histologic outcomes

Variables		8 to 10 week	18 to 20 week	*P* value	95% CI[a]
Vital bone (%)	Mean (SD)	18.17 (8.10)	40.32 (11.30)	<0.0001	(15.55, 28.75)
Residual graft material (%)	Mean (SD)	41.54 (12.01)	23.59 (7.99)	<0.0001	(−24.72, −11.17)
CT/other (%)	Mean (SD)	40.29 (11.13)	36.09 (14.57)	0.33	(−12.89, 4.49)

[a]95% CI of the difference in mean data between short-term and long-term groups.

TABLE 2 Ridge dimensional changes

Variables		8 to 10 week *N* = 19	18 to 20 week *N* = 19	*P* value	95% CI[a]
Change in buccal ridge height (mm)	Mean (SD)	−1.36 (1.23)	−1.00 (0.82)	0.31	(−1.07, 0.35)
Change in lingual ridge height (mm)	Mean (SD)	−0.97 (1.39)	−0.83 (1.00)	0.73	(−0.96, 0.68)
Change in ridge width (mm)	Mean (SD)	−1.00 (1.07)	−1.25 (0.71)	0.42	(−0.86, 0.37)
Baseline ridge width (mm)	Mean (SD)	10.08 (2.25)	10.77 (1.75)	0.30	(−0.64, 2.01)

[a]95% CI of the difference in mean data between short-term and long-term groups.

The study group (8 to 10 weeks) healed for an average of 66.21 days (SD = 5.65) whereas the control group (18 to 20 weeks) healed for an average of 134.74 days (SD = 4.51). Fisher's exact test did not find a significant difference ($P = 0.30$) between the two groups with regard to initial ridge width. The 8 to 10 week group had a mean initial ridge width of 10.08 mm (SD = 2.25), whereas the 18 to 20 week group was 10.76 mm (SD = 1.75). The mean buccal plate thickness at time of extraction for the 8 to 10 week group was 1.04 mm (SD = 0.50), whereas the 18 to 20 week group was 1.17 mm (SD = 0.76), with no significant difference was between groups ($P = 0.50$).

3.1 | Histologic observations

Table 1 summarizes the histomorphometric analysis of the two groups. There was a significantly smaller percentage of vital bone ($P < 0.0001$) in the 8 to 10 week compared to the 18 to 20 week group. Conversely, there was a significantly greater percentage of residual graft ($P < 0.0001$) in the 8 to 10 week group compared to the 18 to 20 week group. Mean percent CT/other was not significantly different ($P = 0.33$) between the two groups.

3.2 | Dimensional changes

There was no statistical difference between the two groups with respect to morphological changes of the alveolar ridge (Table 2). Change in ridge width was similar between groups, with a mean loss of 1.0 mm and 1.3 mm in the short-term and long-term healing groups, respectively ($P = 0.42$). Likewise, there was no significant difference between groups in loss of ridge height on the buccal ($P = 0.31$) or palatal/lingual ($P = 0.73$).

3.3 | Correlations

There was no significant Pearson correlation found between the percentage of vital bone formation and alveolar ridge dimensional changes including: ridge width ($P = 0.66$), buccal height ($P = 0.36$), and lingual/palatal height ($P = 0.45$). There was no significant correlation between baseline buccal plate thickness and change in ridge width ($P = 0.91$). In addition, there was not a significant group-interaction influence between mean percent vital bone in anterior versus posterior sites, sites in maxillary versus mandibular arches, and presence or absence of a dehiscence ≤50% of the socket. There was also no significant correlation between percent vital bone formation and specific patient attributes. The number of subjects who smoked or who had diabetes was small, and there was no correlation between percent of vital bone and the smoking status ($P = 0.77$) or diabetes status ($P = 0.76$) of the patients.

4 | DISCUSSION

The trend in modern implant dentistry is shorter healing times between dental implant placement and implant crown restoration. With that is mind, some clinicians place implants as early as 8 to 10 weeks post ridge preservation, but with limited knowledge of the exact contents of the healing socket.[12] Consequently, the primary objective of this study was to compare two common timepoints after ridge preservation to determine the amount of vital bone formation using a 70%/30% combination allograft. There was a statistical difference in the amount of vital bone formation between the short-term (8 to 20 weeks) and long-term (18 to 20 weeks) groups.

The authors' research group[11–18] previously implemented a similar study design which aids in decreasing the number

of confounding variables and provider bias. This was accomplished by: (1) making custom acrylic stents to allow for repeated measurements at a fixed reference point; (2) obtaining the 70%/30% combination allograft from one single donor; (3) randomization into either the short-term or long-term groups only after measurements and grafting had been completed; (4) only allowing teeth into the study which had the appropriate root angulation for an ideal implant position and which had socket depth of at least 10 mm to ensure the 8 mm core did not contain any native alveolar bone; and (5) each patient receiving the exact same materials and the same post-operative instructions and follow-up. Using bone allograft from a single donor ensured that each bone graft would have the same bone inductivity score and percentage of residual calcium in both treatment groups.

Whetman and Mealey[12] compared ridge preservation with 100% DFDBA at the same time points as the current study. Intuitively, using a higher percentage of DFDBA than the current study should result in a higher percentage of vital bone at both the short and long time points because of the osteoinductive properties of DFDBA. Whetman and Mealey[12] found a mean of 47.4% vital bone at 18 to 20 weeks compared to 40.3% in the current study. Furthermore, Whetman and Mealey[12] found 36.3% vital bone at 8 to 10 weeks compared to only 18.2% in the current study. In both studies, the longer the graft particulate was allowed to heal, the more vital bone was present. However, there was a much greater difference in vital bone in the study using 100% DFDBA[12] compared to the current study using the 70%/30% mineralized/demineralized combination graft. In the study by Wood and Mealey[11] at 18 to 20 weeks of healing, 24.6% mean vital bone was found when using 100% FDBA. It is interesting to note that among the three groups (100% FDBA[11], the current study with 70%/30% FDBA/DFDBA, and 100% DFDBA[12]), the higher proportions of DFDBA yielded a higher percent vital bone when sockets were allowed to heal for 18 to 20 weeks.

Borg and Mealey[13] examined ridge preservation using 100% FDBA compared to the same combination allograft (70%/30%) as the current study and allowed for an average of 19 weeks of healing. FDBA yielded a mean vital bone of 24.7%, whereas the combination 70%/30% allograft yielded 36.2%, which is like the current study's long-term group at 40.3%. It would appear that incorporating more DFDBA into the graft material yielded a higher percentage of vital bone which may be attributed to a higher potential for osteoinductivity. The osteoinductivity of DFDBA has been shown to vary with the age of the donor[8] and the percent of residual calcium present[9]. In the study of Borg and Mealey[13], graft was obtained from a 64-year-old male donor, with an osteoinductivity score of 3 on a 4-point scale, whereas the donor in the current study was an 18-year-old male with an inductivity score of 2 and 3 on the same 4-point scale.

It is clear from the current study and other ridge preservation studies akin to it, that the longer one waits to re-enter a grafted site, the more potential for graft turnover, which histologically translates to a higher amount of vital bone formation. The authors have not encountered a study that relates the amount of vital bone to implant success, failure or complications. Bone quality can affect not only the ratio of bone-to-implant contact, but also an implant's clinical stability at time of placement.[19] A significant amount of residual graft particles was present at 8 to 10 weeks compared to the long-term group in the current study, 41.4% and 23.6%, respectively. Although it is difficult to determine bone quality through drilling of an osteotomy, it is the authors' observation that the bone from the short-term group was more frequently of a less-dense quality, and not yet fully incorporated into the native bone, when compared to the group with longer healing. With an average of 9 weeks of healing, there is, in theory, more "residual graft particles-to-implant" contact than there is vital bone-to-implant contact. The authors have not found any ridge preservation literature that explores the amount of time needed for particulate bone allograft to be fully replaced with new vital bone. Futures studies are needed to explore the relationship between percent vital bone, bone-to-implant contact, implant stability, and implant success.

5 | CONCLUSION

There was more than twice as much vital bone formation after ridge preservation was performed in a non-molar extraction socket using a 70%/30% combination allograft at a healing time of 18 to 20 weeks compared to 8 to 10 weeks. Additionally, there was no difference found in the morphological dimensions of the ridge when comparing the short-term and long-term healing groups.

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AUTHOR CONTRIBUTIONS

Both authors have made substantial contributions to conception and design of the study. ACN and BLM were involved

in data collection, analysis and interpretation as well as writing and revising the manuscript. Both authors have given their final approval of the version to be published.

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