Histological and dimensional changes of the alveolar ridge following tooth extraction when using collagen matrix and collagen-embedded xenogenic bone substitute: A randomized clinical trial

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Abstract

**Aim:** To assess the horizontal and vertical dimensional changes of the alveolar ridge when using a collagen matrix in combination with collagen embedded xenogenic bone substitute, in comparison with natural healing after tooth extraction.

**Methods:** Patients that required extraction in non-molars areas were included. Test group-15 sockets were treated with deproteinized bovine bone mineral containing 10% collagen (DBBM-C), covered by a procaine collagen membrane (CMXs). Control group-15 sockets left for spontaneous healing. We used a custom-made acrylic stent as a reference for alveolar ridge measurements. Six-month postoperative, a single implant was placed in the experimental site. A core biopsy was taken from the site, using a trephine bur. Histomorphometric analysis assessed bone area, connective tissue, bone marrow, and residual bone graft.

**Results:** Six months later, horizontal ridge width at $−3$ mm showed a significant ($p < 0.05$) reduction in both groups albeit smaller in the test group $1.19 ± 1.55$ mm, compared with the control $2.27 ± 1.52$ ($p = 0.087$). At $−5$ mm sub-crestally, statistically non-significant reduction was noted in both groups, $1.61 ± 1.53$ and $1.96 ± 1.52$ mm for the test and control groups, respectively ($p = 0.542$). Vertical changes were smaller in the test group ($0.14 ± 1.84$ mm) compared with control ($0.98 ± 1.49$ mm). Keratinized tissue (KT) width was $7.3 ± 2.13$ and $7.5 ± 3.49$ mm in the test and control groups, respectively. Newly formed bone occupied $33.79 ± 17.37\%$ and $51.14 ± 23.04\%$ in the test and control groups, respectively ($p = 0.11$). Connective tissue volume was $33.74 ± 13.81\%$ and $30.12 ± 18.32\%$ in the test and control groups, respectively ($p = 0.11$). Bone marrow occupied $19.57 ± 10.26\%$ and $18.74 ± 17.15\%$ in the test and control groups, respectively ($p = 0.91$). Residual graft occupied $12.9 ± 9.88\%$ in the test group.

**Conclusion:** Alveolar ridge preservation using DBBM-C resulted in reductions of the vertical and horizontal dimensions albeit not reaching statistical significance. The

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larger than anticipated standard deviation and smaller inter-group differences might account for this phenomenon.

**KEYWORDS**

alveolar ridge dimensions, alveolar ridge preservation, collagen embedded xenogenic bone substitute, core biopsy, non-molars area

**What is known**

Ridge preservation after tooth extraction is a well-known and documented procedure in the dental scientific literature. There is a wide variety of grafting materials and surgical methods. Hence, the decisions about material and way of usage should be based on clinical and histological research.

**What this study adds**

This study is the first randomized controlled clinical trial, which collected both clinical and histological data on alveolar ridge preservation combined therapy in humans, using DBBM-C covered by a procaine collagen membrane (CMXs).

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1 | INTRODUCTION

Alveolar ridge preservation (ARP) is a well-documented surgical procedure associated with tooth extraction designed to attenuate ridge volume diminution.\(^1\) Alveolar bone resorption following tooth extraction was already documented in 1967.\(^2\) Later, Osburn in 1974 introduced the idea that teeth roots can maintain ridge volume beneath removable dentures, hence the term ridge preservation was introduced.\(^3\) The usage of bone grafts in fresh sockets for ARP was introduced in the 1980s.\(^4\) With time, different ARP procedures evolved, using different bone substitutes, as allografts,\(^5\) alloplasts,\(^6\) and xenografts\(^7\) and xenografts embedded in collagen.\(^8\)

Free autogenous connective tissue grafts are sometimes used to seal the extraction sites; while this procedure is considered beneficial, it is somewhat unpredictable.\(^7\) On the other hand, coronal flap advancement to achieve primary closure of the grafted socket does not yield better results over a flapless approach.\(^9\) Likewise, Oghi and Steveling\(^10\) reported no difference between atraumatic extraction and socket seal surgery.

Collagen matrix is a barrier material, which can be left exposed to the oral cavity, while sealing the grafted socket, results in good re-epithelialization during 6-month healing period.\(^11\) Using this kind of material, makes the procedure easier and safer, as there is no need in harvesting connective tissue graft. It was also found beneficial for minimizing ridge resorption and maintaining the soft tissue.\(^12\) We therefore hypothesize that combining collagen matrix with bone graft will improve the results of ridge preservation.

The purpose of this study was to assess the post-extraction horizontal and vertical dimensional changes of the alveolar ridge treated with collagen embedded xenogenic bone substitute covered with collagen matrix and compare it to natural healing.

2 | METHODS

The study was designed as a prospective randomized controlled clinical trial. This study has been independently reviewed and approved by the Rambam Health Care Campus Research Ethics Committee (approval IRB no. 0507-17-RMB) and registered prior to commencement on clinicalTrials.gov NCT# 03395145.

All participants provided written informed consent prior to enrolment in the study.

3 | SAMPLE SIZE AND POWER CALCULATION

Power calculation based on the detection of estimated alveolar ridge reduction, 6 months post-extraction, of 3.2 mm in mean in the control group and 2 mm in the test group, with a standard deviation of 1.1 mm,\(^13\) with an alpha error defined to 0.05 and beta error to 0.20 (power 80%), revealed that 13 subjects in each treatment group were required. Assuming a dropout of 15%, a total of 30 patients were recruited.

3.1 | Study population

Patients were recruited at the department of periodontology, school of dentistry at Rambam health care campus, from May 2018 to August 2020. Patients who required extraction and implant installation in non-molars areas, were initially recruited to the study using the following criteria: at least 18 years old and in need for tooth extraction in the premolar, canine or incisor area with no/minimal (up to 4 mm) bone dehiscence limited to one bony wall only. Patients were excluded if they were pregnant, lactating or
demonstrated incapacity to complete or understand the informed consent process. Also excluded were patients who used medications that affected bone metabolism, heavy smokers (>10 cigarettes a day), patients with dental conditions which might affect the treated site and patients with allergy to collagen.

Prior to the study, all patients underwent clinical and radiographic examination and received periodontal treatment as needed.

After tooth extraction, a single operator (EG) assessed the extraction socket for intact socket walls to determine final eligibility. Patients then signed an informed consent and were randomly allocated into one of two groups using Research Randomizer 4.0 software (Social psychology network), operated by the department research coordinator (LE):

1. Test group-15 sockets to be treated with deproteinized bovine bone mineral containing 10% collagen (DBBM-C; Bio-Oss Collagen, Geistlich Pharma AG, Wolhusen, Switzerland), covered by a procaine collagen membrane (CMXS; Mucograft seal Geistlich Pharma AG, Wolhusen, Switzerland).
2. Control group-15 sockets left for spontaneous healing. Patients remained blinded to the procedure and were not informed for their allocation all along the research period. Clinical and histological data were collected by another researcher, who remained blinded to patients allocation till opening end.

### 3.2 Surgical procedure

Patient received 2 g amoxicillin (600 mg of clindamycin for patients allergic to penicillin) prior to the procedure. Under local anesthesia, the tooth was extracted without flap elevation, attempting to minimize damage to the socket walls.

The following measurements were performed using a custom-made omnivac stent: (a) Alveolar crest height (ACH) measured from the apical border of the stent to the bone crest at the Mesio-Distal midpoint of the socket. (b) Socket width (buccal-lingual aspect) at −3 and −5 mm. (c) Buccal and lingual/palatal thickness of cortical plates at −3 and −5 mm. (d) Keratinized tissue (KT) width measured from the buccal muco-gingival line to the mid-crestal line.

In test group, the surgeon filled the socket with DBBM-C and covered it with CMXS. 5-0 nylon sutures were used to secure the CMXS and get complete seal of the grafted socket (Figure 1). In the control group, the socket margins were sutured in order to stabilize the blood clot; no attempt was made to get a primary socket closure (Figure 2).

### 3.3 Postoperative protocol

Patients were instructed to use a chlorhexidine 0.2% mouthwash twice daily after tooth brushing for 14 days. Additional antibiotics were prescribed for 7 days (amoxicillin 1.5 g/day or clindamycin 600 mg/day) and analgesics as necessary. Sutures were removed after 10–14 days.

| Test group | Control group |
|------------|--------------|
| Flapless Extraction | (A)          | (B)          |
| Custom-made personal stent | (C) | (D) |
| DBBM-C inserted into the extraction socket | (E) | |
| CMXS application, covering the bone graft | (F) | |
| Sutures | (G) | (H) |

**FIGURE 1** Surgical procedure: (A, B) A-traumatic tooth extraction. (C, D) Custom-made personal stent, served as a fixed reference point for the measurements at T1 and T6. (E) Test group was treated with DBBM-C. (F) The grafted socket was covered by a procaine collagen membrane (CMXS). (G) The CMXS was fixed by 6 simple 0-5 nylon sutures. (H) In the control group, extraction sockets were left for spontaneous healing. 4-0 silk sutures were used in order to stabilize the blood clot. DBBM-C, deproteinized bovine bone mineral containing 10% collagen.
3.4 | Implant placement

Six-months postoperative, a CBCT was obtained and a single implant was installed in the experimental site. All implant surgeries were performed by the same clinician (EG).

After signing informed consent for surgical procedure, patient received antibiotic preoperative as described above. KT width was measured at the post-extraction site. A muco-periosteal flap was elevated and intraoperative measurement were repeated at the same site, using the same stent. All measurements were performed by a single examiner (EM).

Next, a core biopsy from the center of the site was taken using a 2.2 mm diameter trephine. The bone samples were processed for histological evaluation of percentage of vital bone, connective tissue, and residual bone graft. Sites were further prepared, using the surgical kit drills, and a bone level titanium alloy implant were installed.

Implant insertion torque was measured with a dental implant torque wrench ratchet (in N/cm²). Resonance frequency analysis (RFA) was measured using Osstell IDx (Osstell, Göteborg, Sweden). Three successive measurements were reordered for each implant and the mean calculated and recorded (Figure 3). Finally, periapical orthoradial X-rays were taken.

Postoperatively, patients were instructed to rinse with 0.2% chlorhexidine for 10 days twice daily, continue their antibiotics for 7 days and use analgesics as needed. Sutures were removed after 10–14 days. Adverse events (AE) and severe adverse events (SAE) cases were monitored and recorded throughout the study. Final restorations were delivered 3–6 months postoperative.

3.5 | Histologic and histomorphometric analysis

All specimens were fixed in 4% paraformaldehyde for 2 days, decalcified in 10% EDTA, for 4 weeks. Samples were dehydrated and washed with ethanol baths in increasing concentrations, in order to remove residual water, afterwards Xylol (hydrophobic agent) was used to remove alcohol remains. Samples were infiltrated with paraffin wax and were...
sectioned by a steel knife mounted in a microtome (Leica RM 2135, Jung RM 2065; Leica Microsystems, Wetzlar, Germany) to a thickness of 8 μm and the sections were mounted on a glass microscope slides using paraffin section mounting bath (Electron Microscopy Sciences, Hatfield, England). Sections underwent hematoxylin and eosin staining. Histomorphometric evaluation of the socket region was performed under a light microscope (Zeiss Axio-skop; Carl Zeiss, Jena, Germany). Images were analyzed using software (ImageJ; National Institutes of Health, Bethesda, MD). (1) Total bone area, (2) connective tissue, and (3) residual bone graft (in the test group) were evaluated and expressed as percentages from the total area.

### 3.6 Satisfaction and pain assessment

Immediately after completion of each surgical procedure (at T1 and T2), the clinical research coordinator gave all the patients a visual analog scale (VAS) assessment form. Patients were instructed to grade their overall satisfaction and intraoperative pain. VAS rulers were graded in a linear scale from 0 to 10.

| Group                      | DBBM + CMXS | Control | p value |
|----------------------------|-------------|---------|---------|
| Number of patients enrolled | 15          | 15      |         |
| Number of patients withdrawn | 1           | 1       |         |
| Age                        | 61.33 ± 14.95 | 63.13 ± 12.23 | 0.72   |
| Gender (female/male)       | 9/6         | 10/5    |         |
| Tooth position (C, P1, P2)  | 0/7/8       | 2/7/6   |         |
| Smokers (≤ 10 c/day)       | 1           | 0       |         |
| Horizontal alveolar ridge width at 3 mm (T0) | 7.4 ± 1.51 | 7.67 ± 1.8 | 0.66   |
| Horizontal alveolar ridge width at 5 mm (T0) | 8.13 ± 1.43 | 8.4 ± 1.67 | 0.64   |
| Cortical buccal bone plate with at 3 mm | 0.94 ± 0.54 | 1.5 ± 1.41 | 0.16   |
| Cortical buccal bone plate with at 5 mm | 1.26 ± 0.63 | 1.57 ± 1.6 | 0.5    |
| Cortical palatal/lingual bone plate with at 3 mm | 1.2 ± 0.55 | 2.02 ± 1.99 | 0.16   |
| Cortical palatal/lingual bone plate with at 5 mm | 2.29 ± 1.01 | 2.14 ± 1.13 | 0.73   |

Abbreviation: DBBM, deproteinized bovine bone mineral.

### 3.7 Statistical analysis

The primary outcome variables were changes in horizontal ridge width at −3 and −5 mm. Secondary outcome variables were changes in ACH, KT width, percentages of new bone formation and residual graft, and implant primary stability. SPSS Advanced Statistics software (IBM) was employed for this statistical analysis, include both descriptive statistics and non-parametric test to compare changes baseline to 6 months in each group and the comparison between groups.

### 4 RESULTS

Thirty patients (11 males and 19 females) enrolled in the study, of which 28 patients (14 in each group), completed the 6-month follow-up, two patients were withdrawn from the study because they did not show up to the 6-month visit (Figure 2). Mean age of participants was 62.23 ± 13.45 years (range: 37–93 years). Only one participant was a smoker (<10 cigarettes a day). There were no

| TABLE 1 | Patient characteristics |
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Abbreviation: DBBM, deproteinized bovine bone mineral.

Note: Test group: extraction sockets filled with deproteinized bovine bone mineral with 10% collagen and covered with a native bilayer collagen membrane; control group: naturally healed sockets. Abbreviation: KT, mean keratinized tissue width.

| TABLE 2 | Alveolar ridge dimensional changes |
|---------|-----------------------------------|
| Test group (n = 14) | Control group (n = 14) | p value |
| Horizontal alveolar ridge width changes at 3 mm | −1.19 ± 1.55 | −2.27 ± 1.52 | 0.087 |
| Horizontal alveolar ridge width changes at 5 mm | −1.61 ± 1.53 | −1.96 ± 1.52 | 0.542 |
| Vertical alveolar ridge changes | 0.14 ± 1.84 | 0.98 ± 1.49 | 0.200 |
| KT | 7.5 ± 3.49 | 7.3 ± 2.13 | 0.840 |
| Distribution of implant diameter (3.3/3.75/4.2) | 0/13/1 | 1/11/2 |
| Successful implant placement | 13b | 14 |
| Need for bone augmentation at the time of implant placement | 1c |

Note: Test group: extraction sockets filled with deproteinized bovine bone mineral. Control group: naturally healed sockets.

aImplant did not get primary stability because of low bone quality (type 4).
bTranscrestal sinus floor augmentation.
cBuccal augmentation in order to cover a buccal dehiscence.

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significant differences between the groups in all baseline parameters (Table 1).

All sites healed uneventfully after tooth extractions. At T6, implant placement was possible in all but one test group patient that exhibited low bone quality at the anterior maxilla. One implant in the test group required trans-crestal sinus floor augmentation and one implant in the control group required minimal augmentation to cover a buccal 2 mm dehiscence measuring.

Horizontal ridge width at −3 mm showed a reduction from T0 to T6 in both groups albeit smaller in the test group (1.19 ± 1.55 mm) compared with the control (2.27 ± 1.52; \( p = 0.087 \); Table 2).

Likewise, at −5 mm, a statistically significant reduction from T0 to T6 was noted in both groups at the 5 mm level (1.61 ± 1.53 and 1.96 ± 1.52 mm for the test and control groups, respectively); however, with no intergroup differences (\( p = 0.542 \)). ACH changes were smaller in the test group (0.14 ± 1.84 mm) compared with the control (0.98 ± 1.49 mm); however, these differences did not reach statistical significance (\( p = 0.2 \)).

The thickness of the cortical buccal plate at −3 mm was slightly wider in the control (1.54 ± 1.41 mm) compared with the test group (0.94 ± 0.54 mm), \( p = 0.16 \). Similar pattern was found at −5 mm (1.57 ± 1.6 and 1.26 ± 0.63 mm, respectively, \( p = 0.5 \)). The palatal plate at −3 mm was thicker in the control (2.02 ± 1.99 mm) compared to the test (1.2 ± 0.55 mm), yet, this difference did not reach statistical significance (\( p = 0.16 \)). Likewise, mean baseline palatal plate at −5 mm was 2.14 ± 1.13 and 2.29 ± 1.01 mm, respectively (\( p = 0.73 \)).

At the time of placement, all implants, in both groups, had good initial stability (Table 3). Insertion torque values were 38.1 ± 11.5 N/cm² for the test group and 41.07 ± 7.12 N/cm² for the control group (\( p = 0.43 \)). Likewise, for the RFA measurements mean implant stability quotient (ISQ) values were 67.8 ± 13.1 and 68.84 ± 5.57 for the test and control groups, respectively (\( p = 0.8 \)).

Mean KT width measured at implant placement was 7.3 ± 2.13 mm in the control group and 7.5 ± 3.49 mm in the test group. There was no significant difference between the groups (\( p = 0.840 \)).

Biopsies were successfully taken from all participants. Vital new bone was found at all biopsies. In the test group, residual graft particles were in contact with neighboring new bone (Figure 4). The percentage of newly formed bone in the test group was 33.79 ± 17.37% compared to 51.14 ± 23.04% in the control, although it did not reach statistical significance (\( p = 0.11 \)). Connective tissue volume was 33.74 ± 13.81% in the test group and 30.12 ± 18.32% in the control group (\( p = 0.65 \)). Bone marrow was occupying 19.57 ± 10.26% in the test group and 18.74 ± 17.15% in the control group (\( p = 0.91 \)). Residual graft was found to occupy 12.9 ± 9.88% of the biopsy volume in the test group (Figure 5).

Mean T1 pain score in the control group (1.64 ± 1.7) was significantly smaller than in the test group (3 ± 2.25, \( p = 0.038 \)). While at T2, these mean values were 1.78 ± 1.18 and 2.42 ± 2.2, respectively (\( p = 0.05 \)). The combined effect of time and treatment on pain was analyzed using repeated measures analysis of variance (ANOVA) with time as the within subject factor. There was no significant effect of time (\( p = 0.695 \)). However, on average, patients in the treatment group reported higher pain levels (\( p = 0.043 \)).
TABLE 4  Satisfaction and pain scores at tooth extraction (T1) and suture removal (T2)

|                      | Test group | Control group | p value |
|----------------------|------------|---------------|---------|
| Pain score (T1)      | 3 ± 2.25   | 1.64 ± 1.7    | 0.04a   |
| Pain score (T2)      | 2.42 ± 2.2 | 1.78 ± 1.18   | 0.05b   |
| Satisfaction score (T1) | 9.29 ± 1.3 | 9.64 ± 0.84   | ≥0.05   |
| Satisfaction score (T2) | 9.71 ± 0.47 | 9.79 ± 0.43   | ≥0.05   |

Note: Although mild pain scores were reported, patients in the test group reported higher pain levels. Abbreviation: ARP, alveolar ridge preservation.

aSignificant difference was found at T1, as a result of ARP procedure.
bThis trend continued for 10 days at T2 as well.

Mean satisfaction score immediately after the procedure (T1) was 9.64 ± 0.84 in the control group and 9.29 ± 1.3 in the test group (p ≥ 0.05). Similar scores were reported at T2: 9.79 ± 0.43 and 9.71 ± 0.47, respectively (p > 0.05). The combined effect of time and treatment on satisfaction was analyzed using repeated measures ANOVA with time as the within subject factor. There were no significant effects of time (p = 0.179) nor treatment (p = 0.388). Furthermore, the interaction between the two factors was also not significant, p = 0.496 (Table 4).

5 | DISCUSSION

The present study was designed to explore the use of DBBM-C and collagen matrix for ARP following tooth extraction. As mentioned, according to our inclusion criteria, we included sockets with no/minimal (up to 4 mm) bone dehiscence limited to one bony wall. The rational of combining both DBBM-C and CMXs was to allow a flapless ARP procedure with minimal heterogeneity, which is possible only in well containing sites. When performing ARP in severely compromised socket, raising partial or full thickness flaps will be needed, such a procedure might be considered as a ridge augmentation procedure, rather than ARP. A meta-analysis of six studies with ARP in compromised buccal wall sites, reported a high degree of heterogeneity. In the current study, we focused on sites with atraumatic extraction with minimal soft tissues manipulation. CMXs served as a durable barrier between the grafted socket and the oral cavity for the initial 30 days healing period. The socket sealing was essential to perform a flapless procedure, without any soft tissue manipulation and KT preservation. Meloni et al. reported that porcine collagen matrix showed similar outcomes as epithelial connective tissue graft, without the need for a palatal donor site. More than that, Fickl et al. reported that DBBM and CMXs combination showed less scar tissue formation then DBBM and free gingival graft combination.

Dimensional changes in bone height and width occurred in both test and control groups. The mean reduction in width (~2 mm) was slightly lower compared with data from a meta-analysis by Tan et al. reporting 3.79 ± 0.23 mm (29%–63%) and 1.24 ± 0.11 mm (11%–22%) for horizontal and vertical changes. In a recent similar study which employed the same filling and barrier materials, a mean reuction of 1.43 ± 0.53 mm in the horizontal buccal dimension 4 months after extraction was reported.

Slightly smaller, but not statistically significant, dimensional changes occurred in the grafted group. Atleie et al. in a recent systematic review concluded that ARP may minimize the overall changes in residual ridge height and width 6 months after extraction but the currently available evidence was very uncertain. Furthermore, there is limited evidence to support the clinical benefit of ARP over unassisted socket healing in improving implant-related outcomes despite a decrease in the need for further ridge augmentation during implant placement. Similar findings were recently reported by Jonker et al. To the contrary, Avila-Ortiz et al. reported that across all materials, socket grafting reduced the amount of alveolar bone resorption as compared to tooth extraction alone by 1.99 mm (95% confidence interval [CI] 1.54–2.44), while collagenated bovine xenografts covered with a collagen membrane resulted in slightly less favorable results (mean difference of 1.20 mm).

Our histological results are in accordance with the literature: 33.79 ± 17.37% vital bone at the grafted sites and 51.14 ± 23.04% at sites of spontaneous healing. Similar results (~30% vital bone) were reported by other investigators that used DBBM-C for ridge preservation. In other studies which used particulated DBBM grafts for ARP, the amount of newly formed bone varied from 21.5% after 4–6 months to 43% after 9 months. Vital bone content, as described by Jambhekar et al., a meta-analysis, was 41.07% in non-grafted sites and 38.8% in the test group, reporting 3.79 ± 0.23 mm (29%–63%) and 1.24 ± 0.11 mm (11%–22%) for horizontal and vertical changes. In a recent similar study which employed the same filling and barrier materials, a mean reduction of 1.43 ± 0.53 mm in the horizontal buccal dimension 4 months after extraction was reported.

A study comparing initial implant stability 6 months after ridge preservation, using calcium phosphosilicate putty or DBBM, reported mean insertion torque under 35 N/cm² in both test groups, these results were inferior in comparison to our results. A study which examined the insertion torque of dental implants in the anterior maxilla 4 months after ARP reported that they achieved insertion torque over 35 N/cm² in 75% of the cases. In a recent study by Santos et al., delayed implant placement, 6 months after ridge preservation using DBBM or autogenous mineralized dentin, yielded high initial stability, with a mean ISQ of 77 in both experimental groups. In a study comparing ridge preservation sites grafted with enamel matrix derivatives (EMD) or DBBM-C, in RFA measurements conducted 3 months of healing mean ISQ of 66 was found in the EMD sites and 65 in the DBBM-C sites.

Mean pain scores both immediately after the procedure and at sutures removal were significantly higher in the test group. The higher
pain score in the test group may be explained by the pressure applied while inserting the DBBM-C into the socket, as it was previously found that mechanical pressure may be represented by VAS pain score. Yet in both groups pain scores were in the mild pain range. Likewise, mild pain scores (2.8 VAS) were reported when DBBM and hemostatic gelatin sponge were used for ARP. However, these higher pain scores did not affect patients’ satisfaction, as the VAS scores for satisfaction were similarly high in both groups in both time points.

6 | CONCLUSION

ARP using DBBM-C and collagen matrix resulted in a small reduction of the vertical and horizontal dimensions. These changes were consistently smaller than those for the control, however they did not reach statistical significance. The larger than anticipated standard deviation and smaller inter-group differences might account for this phenomenon.

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AUTHOR CONTRIBUTIONS

Eran Gabay designed, performed all the surgeries, drafted and approved the article, and critically revised. Anat Katorza collected and analyzed the data, drafted and approved the article. Hdar Zigdon-Giladi contributed to histology, data analysis, critical revision, and approval of article. Jacob Horwitz contributed to data analysis, critical revision, and approval of article. Eli E. Elyahu Machtei contributed to design, clinical measurements, statistics, critical revision, and approval of the article.

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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