Tomographic and Histologic Analysis of Different Socket Sealing Approaches for Alveolar Ridge Preservation: A Randomized Controlled Pilot Clinical Trial

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Purpose: To compare different socket sealing approaches for alveolar ridge preservation and assess the dimensional changes and histologic characteristics of soft and hard tissues in a 4- to 6-month period. ***Material and Methods:*** A total of 22 patients with indicated single-tooth extraction in the maxillary nonmolar region were eligible for this study. After CBCT scanning and minimally traumatic tooth extraction, the alveolar sockets were filled with demineralized bovine bone mineral with collagen (DBBM-C) in patients from all groups except for those in the control group. Patients were divided into groups for socket sealing as follows: unsealed/spontaneous healing (control; n = 6), collagen matrix (n = 5), collagen membrane (n = 5), and autogenous graft (n = 6). A second CBCT scan was taken 4 to 6 months after extraction, and a trephine biopsy of soft and hard tissues was collected during implant placement. Tomographic dimensional changes were compared between groups. Intragroup tomographic evaluation and histological analysis were also performed. ***Results:*** Analysis of dimensional changes did not detect differences between the socket sealing groups ($P > .05$). In an intragroup evaluation, the height of the buccal bone and cross-sectional area of the alveolar ridge were significantly lower 4 to 6 months after extraction for the control group ($P = .031$). Histological analysis revealed that the socket sealing approach had no impact on hard and soft tissue formation. ***Conclusion:*** The data from the present study suggest that socket sealing with a collagen matrix, a collagen membrane exposed to the oral cavity, or an autogenous punch graft had no difference in the effects on volumetric maintenance and tissue formation in a period of 4 to 6 months. *Int J Oral Maxillofac Implants 2023;38:226–238. doi: 10.11607/jomi.9709*

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The remodeling process that takes place in the alveolar ridge after tooth removal can lead to volumetric changes and negative esthetic consequences for patients.[1–3] This volumetric reduction is more pronounced in individuals with a buccal bone wall thickness of less than 1 mm, with these cases producing a vertical buccal bone loss of approximately 7.5 mm in the first year after extraction.[4] Since the immediate implant placement alone fails to prevent alveolar bone loss, the application of grafting materials stands out as the main method to reduce postextraction changes to alveolar ridge architecture.[5–7] In this context, autogenous bone showed poor alveolar socket bone volume maintenance compared to xenografts,[8,9] and osteoconductive materials with a low resorption rate have demonstrated satisfactory results in prospective studies.[10–12] Despite the fact that demineralized bovine bone mineral mixed with 10% collagen (DBBM-C) did not show superior bone volume maintenance in postextraction alveolar ridges compared to pure demineralized bovine bone grafts,[13,14] it has been a preferred treatment material due to its ease of clinical handling.

Sealing the fresh alveolar socket is as important as filling it. Socket sealing aims to protect the bone substitute and, ideally, maintain the thickness and quality of soft tissues. Several strategies have been proposed to seal the grafted socket, such as the rotation of palatal

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flaps,[15] free autogenous soft tissue grafts,[12,16] provisional crowns,[17] collagen membranes,[11,18,19] and collagen or dermal matrices.[20–23] Nevertheless, there is no consensus concerning the application of materials or techniques.[24] Though soft tissue grafts from the palate are frequently used,[25,26] the morbidity and postoperative discomfort lead many patients to refuse these procedures. Matrices and membranes based on collagen are employed to replace the soft tissue techniques of sealing the alveolar socket. In some cases, the architecture of collagen fibers is similar to both materials.[27] Nevertheless, the purpose of each material is different: Collagen matrices have the potential to replace or stimulate soft tissue regeneration, whereas collagen membranes can act as barriers to selective tissue formation. In addition, collagen matrices usually have a thicker, porous layer that favors blood clot retention, which may lead to keratinized tissue formation.[28,29] Current evidence on the topic does not allow for confirmation of this theory, though.

Systematic reviews have shown that the methodologic diversity between studies does not support a statement on the effect of socket sealing materials on dimensional preservation of the alveolar process or soft and hard tissue formation.[24,30] Randomized clinical trials have demonstrated that socket sealing using collagen matrices and xenogenous bone fillers inside the socket provides adequate results in terms of volumetric alveolar preservation after tooth extraction.[21,31–33] Collagen membranes have also shown satisfactory performance in sealing xenogenous bone grafts into alveolar sockets in preclinical studies,[19] clinical trials,[34] and systematic reviews.[35] However, in most publications, the membranes were covered with surgical flaps. A recent systematic review showed that there is still insufficient evidence to determine the benefits of the use of collagen matrices or membranes to seal the grafted socket when exposed to the oral cavity.[36] Therefore, the aim of this study was to compare the volumetric maintenance and quality of tissue formation of different socket sealing approaches associated with alveolar ridge preservation procedures in the maxillary esthetic zone. The primary endpoint was to analyze the dimensional change for the tomographic parameter height of the buccal bone wall at 4 to 6 months after tooth removal, with the other tomographic parameters (height of the palatal bone wall, cross-sectional area of the alveolar ridge, and thickness of the bone ridge) as secondary endpoints. Other assessed outcomes were the intragroup analysis of tomographic parameters between two time points—before tooth extraction and 4 to 6 months after extraction—and the histologic characteristics of soft and hard tissues collected by trephines immediately prior to dental implant insertion.

MATERIALS AND METHODS

Study Design and Ethical Aspects

This randomized controlled pilot clinical trial was approved on September 2015 by the Research Ethical Committee - Federal University of Santa Catarina (CEPSH – UFSC; Protocol nº 1.065.417), Florianópolis, Brazil. During the recruitment phase of the research, all participants were invited to sign and give their free consent to participate in the study. This investigation was reported according to the CONSORT statement[37] and registered on the Brazilian Register of Clinical Trials (register number: RBR-10nbmqm8).

Participants and Sample Calculation

Patients who indicated the extraction of a single incisor, canine, or premolar located in the maxilla and who were subsequently in need of an implant-supported rehabilitation were eligible for this study. Patient recruitment was carried out between September 2015 and March 2018, and clinical follow-up was performed up to February 2020 at the Federal University of Santa Catarina Center for Education and Research on Dental Implants (CEPID). Based on the analysis of means and standard deviations of tomographic measurements from previous studies,[21,38] the sample size calculation estimated four groups of 10 patients/teeth for statistical relevance (n = 40). However, a subsequent power analysis revealed that approximately 240 patients would be necessary for β = 80%, considering a difference of 0.5 mm between four groups with a standard deviation of 1 mm. Nevertheless, the execution of a study with such a large sample is far beyond the feasibility of this research. Therefore, a pilot clinical trial was proposed, and the number of 10 patients per group was established as a goal. This number is in line with other clinical studies that evaluated alveolar ridge preservation.[21,33,38,39]

Patient Selection

After an initial screening involving anamnesis and physical examination, patients were selected according to the following inclusion criteria: *(1)* age 18 or above; *(2)* the presence of at least 20 teeth in the mouth; *(3)* satisfactory oral hygiene (plaque index ≤ 25%); *(4)* tooth extraction indicated in the maxillary esthetic zone (nonmolar region); *(5)* both adjacent teeth present for interproximal bone crest maintenance; and *(6)* alveolar bone integrity around the tooth (no bone loss in any socket wall) assessed by CBCT and confirmed by postextraction clinical examination.

This study excluded smokers and patients with self-reported systemic conditions such as diabetes and pregnancy. Information from participants who failed to follow the research protocol were excluded to avoid incomplete data.

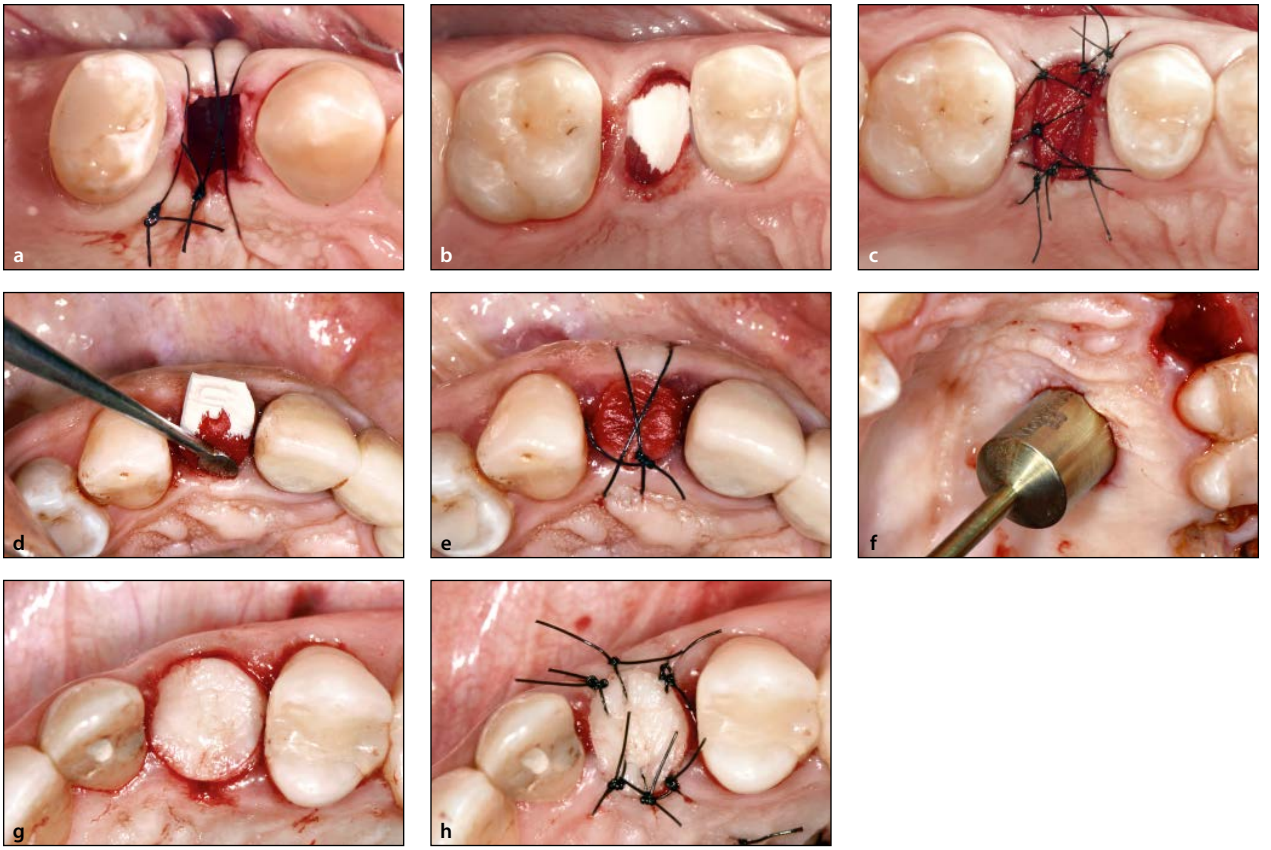


Fig 1 Surgical protocols of the different socket sealing groups. *(a)* The control group did not receive any bone substitute or socket sealing (spontaneous healing). *(b)* In the collagen matrix group, the socket was filled with DBBM-C, followed by *(c)* sealing the socket with the collagen matrix, which was sutured to the adjacent soft tissue. *(d)* In the collagen membrane group, the socket was filled with DBBM-C, followed by *(e)* sealing the socket with the collagen membrane, which was stabilized with compressive sutures and left exposed to the oral cavity. *(f)* A punch graft with an 8-mm diameter was collected from the palate in autogenous graft group, and *(g)* the socket was filled with DBBM-C, with the autogenous graft positioned over the socket before *(h)* being sutured to the surrounding tissues using simple interrupted sutures.

Randomization

A randomization list (block randomization) was obtained through an open access online platform (www.randomization.com) prior to patient recruitment. Participants were consecutively assigned a number from the list, following the random sequence. A researcher (C.A.M.B.) not involved in recruitment or clinical attendance was responsible for keeping the randomization list on a password-protected computer. Other researchers did not have access to the random sequence, which remained confidential until the surgical procedure. The participants were allocated to one of the groups shortly after tooth extraction.

Surgical Protocol

After local anesthesia (2% mepivacaine with epinephrine 1:100,000), flapless extractions were performed as gently as possible using a periotome and a vertical root extractor. Extraction sockets were checked with a periodontal probe for the presence of intact alveolar bone walls after tooth removal and were filled with DBBM-C (Bio-Oss Collagen, Geistlich Pharma) in all groups except for the control group, which did not receive any biomaterial and passed through spontaneous healing. Each participant contributed only one extraction site. Patients were divided into four groups according to socket sealing approach: *(1)* spontaneous healing (control), which used no filling or sealing materials; *(2)* collagen matrix (Mucograft Seal, Geistlich Pharma); *(3)* collagen membrane (Bio-Gide, Geistlich Pharma); and *(4)* autogenous grafting (soft tissue punch graft from the palate).

After stabilization of the sealing materials with compressive or simple sutures (monofilament nylon suture 5-0), the dental prostheses were adjusted to avoid biomaterial or soft tissue pressure. One professional (G.L.M.) with more than 5 years of clinical experience in implant dentistry performed all surgical procedures (Fig 1).

Postoperative Care

Patients were instructed to use extraoral cold compresses on the operated areas during the first 24 hours

after surgery, follow a soft and cold diet for the first 2 days, avoid physical efforts for a week, and perform dental hygiene carefully in the surgical site until the sutures were removed. All patients received the same medication protocol (Amoxicillin 500 mg every 8 hours for 7 days, Ibuprofen 600 mg every 12 hours for 3 days, and chlorhexidine digluconate 0.12% every 12 hours for 7 days) except for a patient who was allergic to penicillin, who received clindamycin 300 mg every 8 hours for 7 days instead of Amoxicillin. The surgical sites were evaluated in the postoperative period at a minimum of two time points: at 2 weeks for suture removal and at 4 months for implant planning.

Biopsy Collection and Implant Placement

Dental implants were placed 4 to 6 months after tooth extraction and alveolar ridge preservation. Surgical planning was performed individually, with consideration of the tomographic measurements. During the implant surgery, a circular punch incision was made, followed by the initial perforation of the alveolar ridge, which was performed via a flapless approach using a 3-mm–diameter trephine drill in order to collect a biopsy of soft and hard tissues for histologic analysis. Biopsies were immediately immersed in 10% neutral buffered formalin solution. The implant bed was prepared according to the planned measures of each case, following the protocol described in the surgical manual of the implant system (Strong SW, S.I.N. Implant System). Healing abutments or cover screws were installed according to the implant mechanical stability, which was measured with a torque wrench during implant placement. Insertion torque values ≥ 30 Ncm were suitable for healing abutments. No sutures were needed. One professional (G.L.M.) performed all biopsies and implant surgeries.

Tomographic Analysis

Patients had CBCT scans performed with a standardized scanner (PreXion 3D) at two time points: prior to tooth extraction (baseline) and 4 to 6 months after the extraction. Tomographic scans were used for the dimensional analysis of hard tissues and surgical planning of extractions and dental implants. To assist the positioning of coincident tomographic sections at different time points, an acrylic resin tomographic guide was made on a stone model of the patient maxilla. An approximately 8-mm–long cross-shaped preparation was carried out in the facial part of the guide with a conical drill, and a barium sulfate radiopaque liquid (Glaze TDV) was applied in this area. CBCT scans were performed with the following settings: 90 kV, 4 mA, field of view = 5 × 6 cm, exposure time = 33.5 seconds, and voxel size = 0.099 mm.

Tomographic exams were exported to the AxioVision software (Zeiss), where the area of interest was selected and the measurements were performed. The central sagittal section of the socket (in the mesiodistal aspect) was identified in each CBCT, and the tomographic guide was used to check the coincident points at baseline and the 4- to 6-month exams. The scaling wizard tool was employed to create a scale for each tomographic section, using the real size scale of the CBCT as a reference. A modified version of the methods applied by Araújo et al[38] and Misawa et al[40] was employed for tomographic measurements. First, a line connecting the center of the tomographic guide and the apical central point (ACP) of the alveolar socket was made. Another line, perpendicular to the bisector plane that divides the socket in half, was traced on the apical extension of the alveolar socket, from the buccal point (BP) on the buccal bone plate to the palatal point (PP) on the palatal bone plate, crossing the ACP. Four tomographic measurements were obtained:

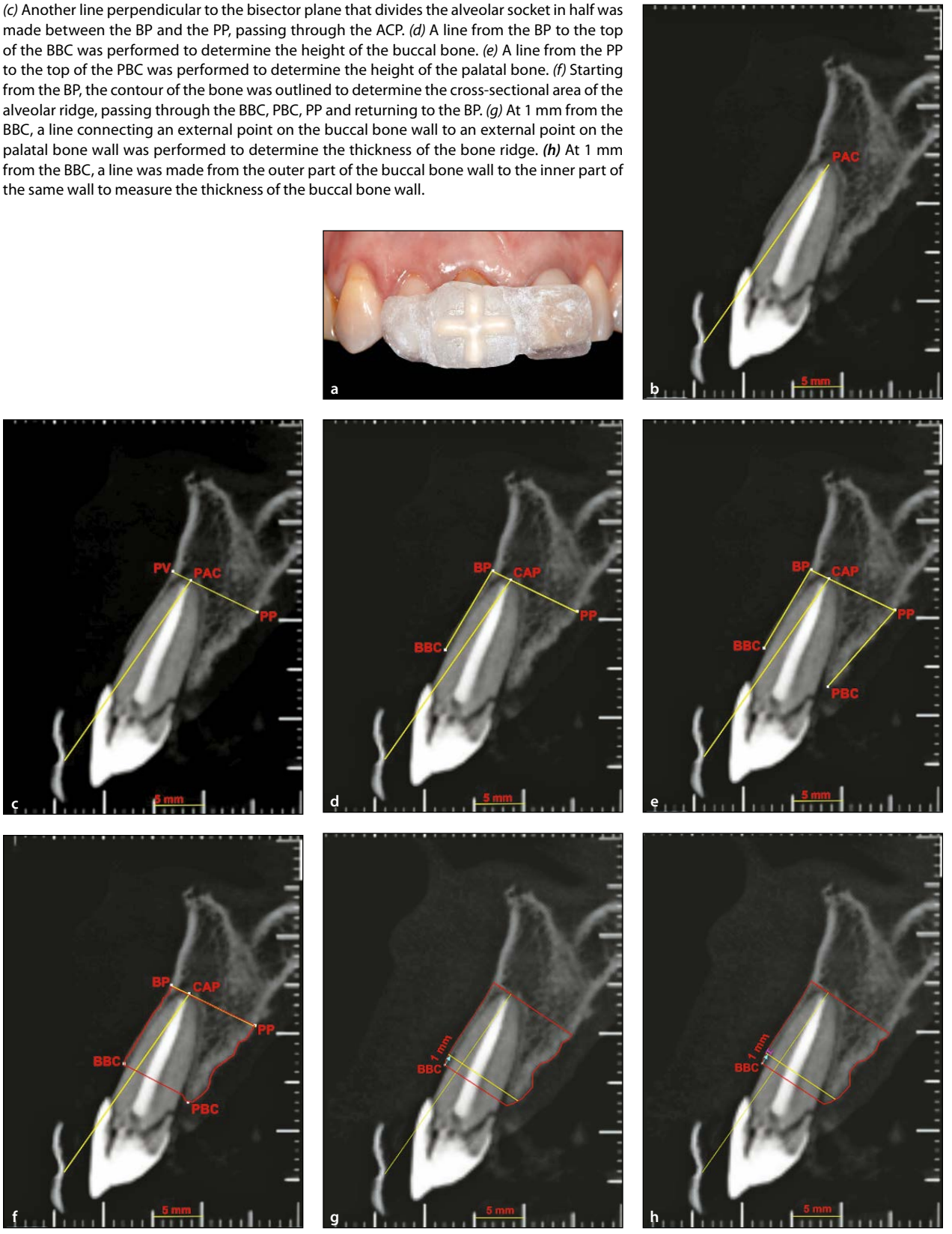
1. The height of the buccal bone, measured in mm by a vertical line from the BP to the top of the buccal bone crest (BBC);
2. The height of the palatal bone, measured in mm by a vertical line from the PP to the top of the palatal bone crest (PBC);
3. The cross-sectional area of the alveolar ridge, corresponding to the area below the apical extension of the alveolar socket. To obtain this measure, the contour of the alveolar process was outlined, starting from the BP and passing through the BBC, PBC, and PP before returning to the origin. The area inside this perimeter was calculated by the software in mm^2;
4. The thickness of the bone ridge, measured by a buccopalatal line 1 mm from the top of the BBC.

The dimensional change was calculated by the difference between measurements obtained at baseline and at 4 to 6 months, and these values were compared between groups. The tomographic parameters were also analyzed via intragroup comparison at the two time points. Because the thickness of the buccal bone wall can influence the bone remodeling process after tooth extraction,[4,41] it was measured at a line 1 mm from the top of the buccal crest on the baseline CBCT scan. This measurement was used to classify the patients as either having thin phenotypes (thickness of the buccal bone wall < 1 mm) or thick phenotypes (thickness of the buccal bone wall ≥ 1 mm). More details are provided in Fig 2.

Histologic Analysis

Biopsies were fixed in a formalin solution for 24 hours and decalcified in 20% EDTA (pH 7.3), with the liquid changed every other day. A pathologist (E.R.C.R.) checked the level of decalcification by testing the

Fig 2 Tomographic analysis. *(a)* A tomographic guide was used to standardize the measurements in both evaluation times. *(b)* The most central cross-sectional tomographic image from the alveolar socket was selected, and a line was made from the center of the guide to the ACP. *(c)* Another line perpendicular to the bisector plane that divides the alveolar socket in half was made between the BP and the PP, passing through the ACP. *(d)* A line from the BP to the top of the BBC was performed to determine the height of the buccal bone. *(e)* A line from the PP to the top of the PBC was performed to determine the height of the palatal bone. *(f)* Starting from the BP, the contour of the bone was outlined to determine the cross-sectional area of the alveolar ridge, passing through the BBC, PBC, PP and returning to the BP. *(g)* At 1 mm from the BBC, a line connecting an external point on the buccal bone wall to an external point on the palatal bone wall was performed to determine the thickness of the bone ridge. ***(h)*** At 1 mm from the BBC, a line was made from the outer part of the buccal bone wall to the inner part of the same wall to measure the thickness of the buccal bone wall.



penetration resistance with a 30-gauge needle. The decalcified samples were embedded in paraffin, sectioned (3 µm thick), and stained with hematoxylin and eosin (H&E). Histologic slides were identified by alphanumeric codes to blind the examiners and were scanned using the Axio Scan.Z1 system (Zeiss) × 20 magnification. Descriptive histologic analysis of the soft tissue was performed by considering the integrity of the epithelial tissue, keratinization of the epithelium, organization of the connective tissue, and presence of inflammatory infiltrate. Descriptive histologic analysis of the hard tissue was performed by considering the characteristics of the newly formed bone (mature or immature), presence of biomaterial, and characteristics of the nonmineralized matrix. The following criteria were used for classification of tissue responses: 0 = inflammation absent, with 0 to 10 inflammatory cells/area; 1 = mild inflammation, with 11 to 25 cells/area; 2 = moderate inflammation, with 26 to 65 cells/area; and 3 = severe inflammation, with > 65 inflammatory cells/area.[42]

After training with an experienced researcher (C.A.M.B.), two examiners (G.L.M. and L.D.S.) were calibrated by Kappa test (intra- and interexaminer) using 20% of the samples. Examiners obtained a K score ≥ 0.7 (great agreement) in two assessments, with 7 days of difference between each one. Examiners analyzed the histologic slides independently, assigning values to the histologic findings in each slide. Cells were counted visually in three different areas of the slides. The examiners compiled their results, and divergences were solved by discussion until mutual agreement or, if persistent, in a consensus meeting with a third party (C.A.M.B.). After finishing the evaluations, the identification of the slides was disclosed for data analysis.

Statistical Analysis

Kruskal-Wallis nonparametric test was applied to verify differences between socket sealing groups for dimensional change in each tomographic parameter (buccal bone height, palatal bone height, cross-sectional alveolar ridge area, and bone ridge thickness). Wilcoxon test was used for intragroup comparisons between evaluation times (baseline and 4 to 6 months). Analyses were performed in the software GraphPad Prism version 7 (GraphPad Software) with a significance level of 5% ($P = .05$).

RESULTS

Demographic Aspects

A total of 233 individuals were initially screened, and 55 patients were selected for potential inclusion after anamnesis and clinical examination. Of these, 22 patients were enrolled in this study and underwent tooth extraction and other procedures. The remaining 33 patients were excluded for the following reasons: *(1)* teeth could be treated and did not need to be extracted (n = 3); *(2)* interproximal or palatal bone loss was detected via CBCT scan (n = 7); *(3)* bone loss in the buccal wall was detected via CBCT scan (n = 6); *(4)* patient could not attend consultations (n = 4); *(5)* patient opted for other procedures (eg, immediate implantation) or refused to participate in the research (n = 8); or *(6)* the teeth neighboring the one indicated for extraction included either a condemned tooth or an implant-supported restoration (n = 5). Patients included in the study (n = 22) were randomly allocated to one of the four research groups (control = 6; collagen matrix = 5; collagen membrane = 5; autogenous graft = 6). More details are provided in Fig 3.

All extractions followed the proposed protocol, without complications or damage to adjacent tissues. Complications in the postextraction period were only observed in 1 patient (collagen matrix group), who lost the socket sealing material. However, granulation tissue had already formed in the region, and the patient data was maintained in the research. No patients reported pain in the extraction site, though 2 patients in the autogenous graft group reported pain associated with the donor site in the palate. Of the 14 participants who received provisional crowns attached to neighboring teeth, 12 (85.7%) showed crown loosening in the postextraction period. In all cases, this situation was treated in emergency consultations by either splinting with composite resin or cementation. After a healing period of approximately 5.1 ± 0.8 months, patients were submitted to biopsy and dental implant placement. All performed surgeries were flapless, except for in 1 patient (collagen membrane group), who required a flap to verify the implant placement inside the bone bed. Cover screws were placed in 54.5% of the cases (n = 12) due to low insertion torque (< 30 Ncm). Four implants were lost (18.2% of the cases) before prosthetic loading, consisting of implants from 2 patients in the control group and 2 patients in the autogenous graft group, and new implants were placed. Prosthetic rehabilitation was offered for all participants. More details can be seen in Table 1.

Tomographic Data

A total of 21 participants were included for tomographic analysis. The data from 1 patient in the autogenous graft group were not used because the participant did not follow the research protocol. Due to the method applied, the data of 1 patient in the control group were removed from the bone ridge thickness analysis because the palatal wall did not follow the loss in buccal wall height, which was much more expressive. This discrepancy distorted the distance, which generated a measurement that was not representative of the clinical

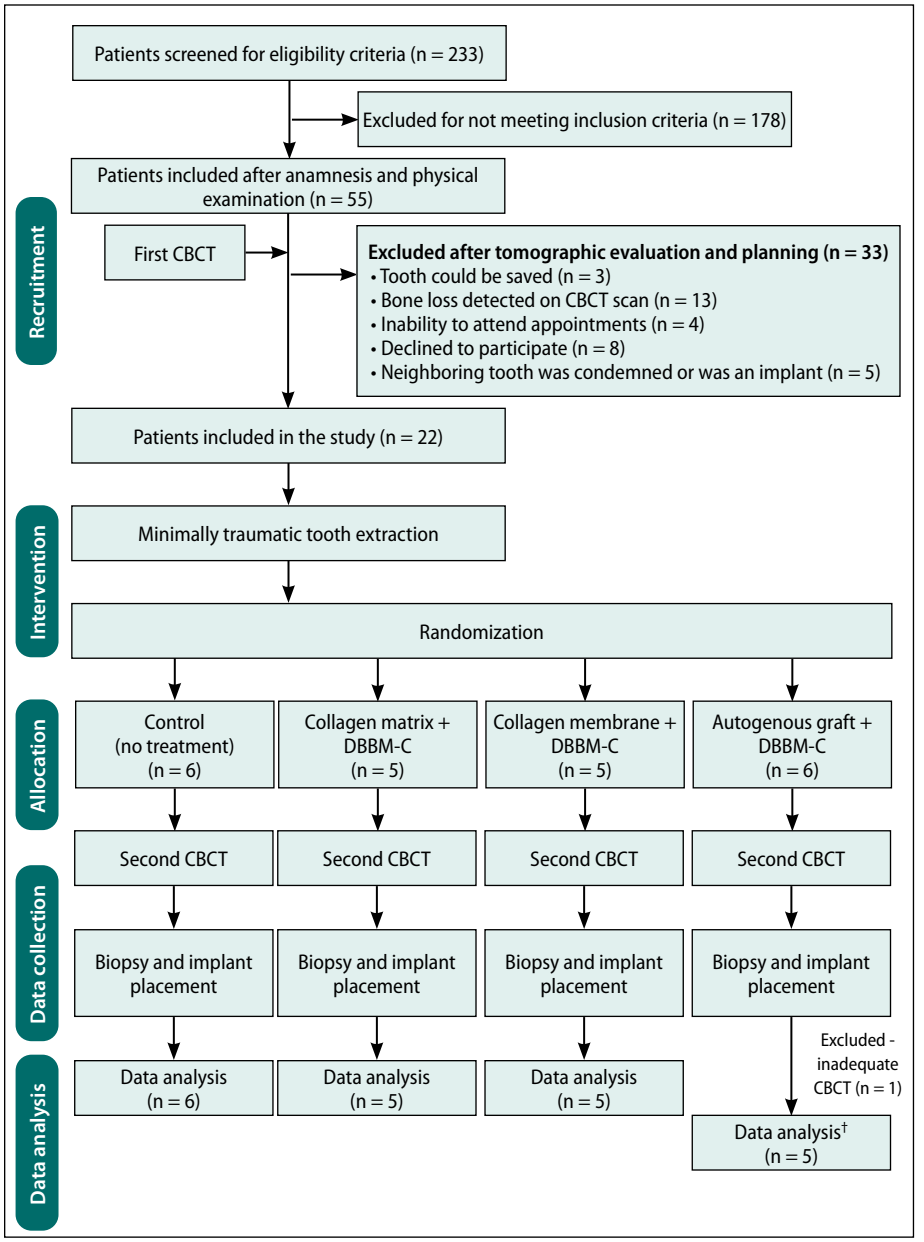


Fig 3 Flowchart of participants included in the research. †Only for tomographic analysis.

Table 1 Demographic Data of Participants

	Control	Collagen matrix	Collagen membrane	Autogenous graft
Included patients	6	5	5	6
Age mean ± SD (years)	45.5 ± 14.0	48.2 ± 12.0	45.0 ± 12.0	41.2 ± 6.7
Female/male	3/3	2/3	4/1	3/3
Incisors/canines/premolars	2/0/4	2/0/3	2/0/3	2/1/3
Implant loss	2	0	0	2

reality of the change in bone ridge thickness. Data analysis of the dimensional change for the buccal bone height, palatal bone height, cross-sectional area of the alveolar ridge, and thickness of the bone ridge did not show statistically significant differences between the four groups of this study ($P > .05$). However, intragroup comparisons between the baseline and 4- to 6-month time points demonstrated a significant difference for

height of the buccal bone and cross-sectional area of the alveolar ridge in the control group ($P = .031$). Other comparisons were not significant (Fig 4). More details are shown in Table 2 and Appendix 1. The thickness of the buccal bone wall showed that 66.7% of the patients (n = 14) had a thin phenotype, while 33.3% (n = 7) had a thick phenotype (control = 3 thin phenotypes/3 thick phenotypes; collagen matrix = 4 thin phenotypes/1 thick phenotype; collagen membrane = 4 thin phenotypes/1 thick phenotype; autogenous graft = 3 thin phenotypes/2 thick phenotypes).

Histologic Evaluation

Trephine biopsies were collected from all participants; however, in one case (autogenous graft group), bone tissue was lost during the surgical intervention and only soft tissue was analyzed. The mean decalcification time was 19.3 ± 12.9 days. After intraexaminer (k = 0.79) and interexaminer (k = 0.72) calibration, two researchers (G.L.M. and L.D.S.) performed the histologic analysis. Three expert researchers (E.R.C.R, R.G., and C.A.M.B.) checked the data and contributed to the interpretation of results.

Epithelial tissue showed similar results for all samples: four epithelial strata (basale, spinosum, granulosum, and corneum), keratinization in the corneum layer, adequate epithelial thickness, and abundant epithelial ridges. The connective tissue was considered dense and irregular, with collagen fibers arranged in different orientations. Most samples showed a mild and chronic inflammatory infiltrate, with moderate to intense presence of blood vessels. More blood vessels were found close to the epithelium or in the presence of an acute inflammatory infiltrate. Four samples (collagen matrix = 3, autogenous graft = 1) showed an acute inflammatory process, characterized by the predominance of neutrophils, moderate to intense presence of blood vessels, the presence of macrophages, and multinucleated giant cells. Two cases (collagen membrane = 1, autogenous graft = 1) revealed biomaterial particles trapped in the connective tissue, which provoked tissue reactions such as fibrosis around the particle and inflammatory activity. The bone tissue was considered immature in most of the samples, characterized by newly formed bone with numerous osteocytes and many residual particles of biomaterial in groups with alveolar socket filler. The nonmineralized matrix consisted of loose connective tissue, which was abundant in blood vessels and poorly organized collagen fibers, as well as a predominance of fibroblasts, the presence of adipose tissue, and few inflammatory cells. One sample (autogenous graft group) from a patient who had early implant loss revealed absence of lamellar bone, a high amount of residual biomaterial, little newly formed bone restricted to the region around the biomaterial, many fibers and cells in the nonmineralized matrix, and a high amount of inflammatory infiltrate, mainly in the transition zone between connective tissue and bone (Fig 5).

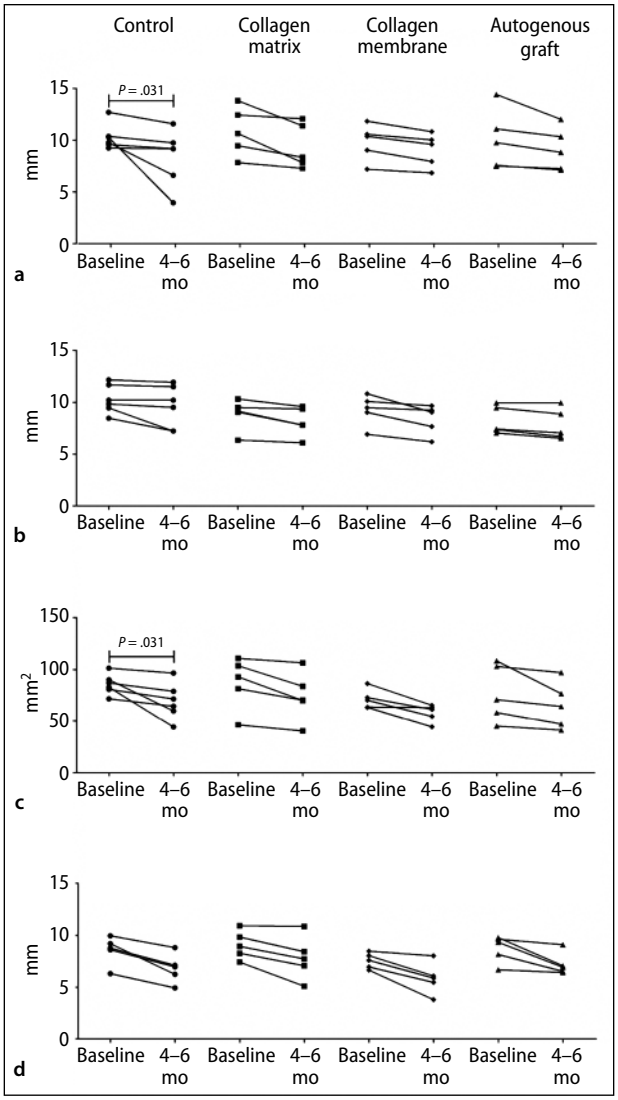


Fig 4 Dot plots showing the tomographic parameters in an intragroup analysis at baseline and 4 to 6 months. *(a)* Height of the buccal bone, *(b)* height of the palatal bone, *(c)* cross-sectional area of the alveolar ridge, and *(d)* thickness of the bone ridge. Differences between time points were detected for the height of the buccal bone and cross-sectional area of the alveolar ridge in the control group. Lines above the graphs indicate the statistically significant differences between evaluation times ($P < .05$).

DISCUSSION

The present study compared different alveolar ridge preservation protocols by varying the socket sealing approach, including spontaneous healing, a collagen matrix, a collagen membrane, and an autogenous graft harvested from the palate. The present findings showed

Table 2 Tomographic Data

Parameter/group		Baseline	4 to 6 months	Dimensional change	Dimensional change (%)	*P* value
Height of the buccal bone (mm)						
Control	Mean ± SD	10.33 ± 1.24	8.38 ± 2.69	−1.95 ± 2.41	−18.97 ± 23.73	.756
	Median	10.04	9.18	−0.87	−7.40	
	Maximum	12.70	11.59	−6.34	−61.60	
	Minimum	9.25	3.95	−0.08	−0.90	
Collagen matrix	Mean ± SD	10.84 ± 2.36	9.39 ± 2.19	−1.45 ± 1.10	−13.14 ± 9.17	
	Median	10.65	8.36	−1.11	−11.70	
	Maximum	13.81	12.07	−2.81	−26.40	
	Minimum	7.84	7.28	−0.37	−3.00	
Collagen membrane	Mean ± SD	9.80 ± 1.76	9.05 ± 1.62	−0.75 ± 0.31	−7.62 ± 2.92	
	Median	10.37	9.60	−0.77	−7.40	
	Maximum	11.84	10.83	−1.09	−12.10	
	Minimum	7.20	6.84	−0.36	−5.00	
Autogenous graft	Mean ± SD	10.07 ± 2.86	9.11 ± 2.09	−0.96 ± 0.85	−8.52 ± 5.01	
	Median	9.77	8.83	−0.75	−6.80	
	Maximum	14.42	12.02	−2.40	−16.60	
	Minimum	7.51	7.12	−0.26	−3.50	
Height of the palatal bone (mm)						
Control	Mean ± SD	10.33 ± 1.39	9.62 ± 2.04	−0.70 ± 0.87	−7.76 ± 9.37	.561
	Median	10.05	9.89	−0.28	−3.45	
	Maximum	12.19	11.96	−2.24	−23.60	
	Minimum	8.49	7.24	−0.02	−0.00	
Collagen matrix	Mean ± SD	8.89 ± 1.50	8.15 ± 1.41	−0.74 ± 0.56	−8.18 ± 5.91	
	Median	9.17	7.82	−0.73	−7.10	
	Maximum	10.34	9.61	−1.35	−14.70	
	Minimum	6.37	6.12	−0.13	−1.40	
Collagen membrane	Mean ± SD	9.29 ± 1.48	8.38 ± 1.43	−0.91 ± 0.65	−9.74 ± 6.26	
	Median	9.50	9.07	−0.73	−10.50	
	Maximum	10.85	9.69	−1.78	−16.40	
	Minimum	6.93	6.20	−0.24	−2.50	
Autogenous graft	Mean ± SD	8.27 ± 1.36	7.84 ± 1.51	−0.43 ± 0.26	−5.22 ± 3.49	
	Median	7.44	7.07	−0.50	−6.40	
	Maximum	9.98	9.96	−0.67	−9.10	
	Minimum	7.05	6.55	−0.02	−0.20	
Cross-sectional area of the alveolar ridge (mm^2)						
Control	Mean ± SD	85.61 ± 9.93	69.25 ± 17.81	−16.36 ± 14.41	−19.28 ± 16.89	.898
	Median	84.94	68.02	−8.63	−10.70	
	Maximum	101.30	96.58	−38.80	−46.80	
	Minimum	71.65	44.14	−4.69	−4.60	
Collagen matrix	Mean ± SD	87.02 ± 25.36	74.16 ± 24.06	−12.86 ± 8.30	−14.88 ± 7.76	
	Median	92.95	70.33	−11.12	−13.70	
	Maximum	110.80	106.50	−23.00	−24.70	
	Minimum	46.24	40.29	−4.35	−3.90	
Collagen membrane	Mean ± SD	71.27 ± 9.46	57.72 ± 8.54	−13.55 ± 8.17	−18.66 ± 11.24	
	Median	70.17	61.29	−15.64	−22.30	
	Maximum	86.46	65.37	−21.09	−30.00	
	Minimum	63.26	44.27	−0.42	−0.70	
Autogenous graft	Mean ± SD	77.11 ± 27.72	65.23 ± 22.64	−11.80 ± 11.51	−14.32 ± 9.81	
	Median	70.87	64.25	−6.17	−8.70	
	Maximum	108.40	97.03	−31.81	−29.30	
	Minimum	45.05	41.19	−3.86	−5.80	
Thickness of the bone ridge (mm)						
Control	Mean ± SD	8.58 ± 1.37	6.82 ± 1.41	−1.76 ± 0.70	−20.68 ± 7.43	.653
	Median	8.79	6.97	−1.65	−19.10	
	Maximum	9.98	8.83	−2.96	−32.10	
	Minimum	6.31	4.94	−1.15	−11.50	
Collagen matrix	Mean ± SD	9.10 ± 1.37	7.84 ± 2.10	−1.25 ± 0.81	−14.94 ± 10.94	
	Median	8.95	7.74	−1.22	−14.50	
	Maximum	10.95	10.88	−2.33	−31.40	
	Minimum	7.43	5.10	−0.07	−0.60	
Collagen membrane	Mean ± SD	7.56 ± 0.76	5.85 ± 1.51	−1.70 ± 0.87	−23.36 ± 13.32	
	Median	7.61	5.88	−1.73	−22.70	
	Maximum	8.49	8.03	−2.86	−42.90	
	Minimum	6.66	3.80	−0.46	−5.40	
Autogenous graft	Mean ± SD	8.73 ± 1.31	7.22 ± 1.09	−1.51 ± 1.10	−16.62 ± 11.27	
	Median	9.35	6.93	−1.63	−20.00	
	Maximum	9.80	9.12	−2.72	−27.80	
	Minimum	6.69	6.43	−0.26	−3.90	

P value based on the dimensional change analysis (difference between baseline and 4 to 6 months evaluations).

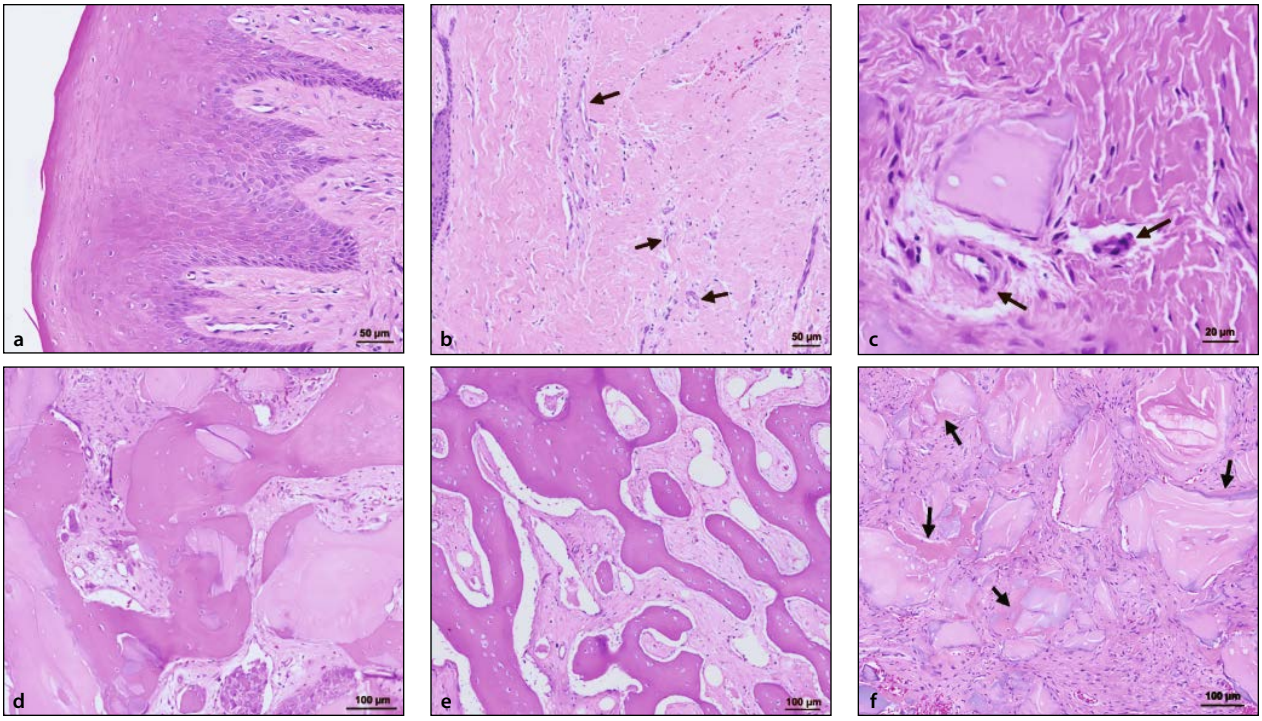


Fig 5 Histologic analysis. *(a)* The epithelial tissue was a squamous stratified epithelium with adequate thickness, abundant epithelial ridges, four epithelial strata (basale, spinosum, granulosum, and corneum), and keratinization in the stratum corneum (H&E, magnification ×20). *(b)* The connective tissue was dense and irregular, with collagen fibers in different directions, and most of the analyzed samples revealed the presence of a chronic inflammatory infiltrate, with light intensity and moderate presence of blood vessels (arrows; H&E, ×20 magnification). *(c)* Biomaterial particles were detected in the connective tissue of two samples, which generated encapsulation by collagen fibers, inflammatory reaction, and vascular formation (arrows; H&E, ×40 magnification). *(d)* Samples with bone fillers inside the sockets showed immature bone, with many biomaterial particles surrounded by newly formed bone (H&E, ×10 magnification). *(e)* Samples from the control group were also characterized by immature bone, wide trabecular space, and loose connective tissue in the nonmineralized matrix (H&E, ×10 magnification). *(f)* In the sample of a patient with early implant loss, the absence of lamellar bone, new bone formation restricted to biomaterial particles *(arrows)*, and many fibroblasts in the nonmineralized matrix (H&E, ×10 magnification) was observed.

no difference between socket sealing protocols concerning the dimensional change over a 4- to 6-month period. The similarity between alveolar ridge preservation groups (collagen matrix, collagen membrane, and autogenous graft) indicates that these socket sealing strategies are very similar with respect to volumetric maintenance, without significant distinction between the treatment modalities. However, a difference with the control group was expected, since no treatment to maintain the alveolar volume was performed. One explanation for this outcome is the sample size, which limited the statistical power. Another explanation is based on the fact that 50% of the patients in the control group had a thick bone phenotype, which exerts a substantial influence on dimensional tissue change after tooth extraction. Thick phenotypes, defined as a buccal bone wall thickness ≥ 1 mm, are less prone to volumetric loss even in the absence of postextraction treatment.[4,41] Although it was not statistically significant in comparison to other groups, the height of the buccal bone wall of the control group had the highest mean dimensional change, the highest standard deviation, and the highest maximum value in terms of loss, approximately 4 mm greater than other groups.

Tomographic analysis comparing the measurements before extraction and 4 to 6 months after extraction revealed a significant difference for the parameters of buccal bone height and cross-sectional alveolar ridge area in sites that healed spontaneously, but not in sites submitted to alveolar ridge preservation. These data confirm the findings of other studies, which found that bone loss was reduced for alveolar sockets treated with bone fillers and socket sealing in comparison to groups without treatment.[11,21,31,38] It is expected that alveolar sockets that heal spontaneously experience a collapse of the alveolar volume due to the resorption of the buccal bone wall,[1] an unavoidable process that is compensated for by the application of slowly resorbing materials inside the socket. Differences were not found for the palatal bone height or the bone ridge thickness, and other factors may be involved in these results. While the palatal bone wall is less susceptible than the buccal wall to dimensional changes after tooth extraction,[1,31,32,40] the thickness of the bone ridge is

generally more pronounced than the vertical bone loss in a 6-month period.[21,23] More investigations are recommended to clarify this topic.

The histologic findings of this research revealed that the soft tissue formation was similar in groups with or without socket sealing. The structure of the collagen matrix did not influence tissue formation as much as the collagen membrane or autogenous graft, and all of these alternatives had a similar clinical and histologic result 4 to 6 months after alveolar ridge preservation. A preclinical study showed that the tissue formed in extraction sites sealed with collagen matrix exposed to the oral cavity was compatible with oral keratinized mucosa after a 12-week healing period.[43] On the other hand, the use of collagen membranes exposed to the oral cavity is controversial. Early membrane degradation with the possible loss of bone grafting and an increased risk of treatment failure has been reported.[44] However, the present research demonstrated that socket sealing via collagen membranes exposed to the oral cavity is viable and that the soft tissue formed in the region is suitable for subsequent treatment with dental implants. Other studies have also evaluated the application of collagen membranes to seal the alveolar socket exposed to the oral environment. A clinical study with 11 molar sockets filled with DBBM-C showed that socket sealing with one or two layers of collagen membrane exposed to the oral cavity was effective at preserving the bone volume of the alveolar ridge and allowed for dental implant placement after 4 months of healing.[45] A randomized clinical trial compared three different approaches in molar sites: socket filling with DBBM-C and socket sealing via collagen membrane exposed to the oral cavity, socket filling with DBBM-C without sealing, and spontaneous healing of the alveolus.[46] Results after 4 months demonstrated less horizontal bone resorption in the collagen membrane group compared to the spontaneous healing group and less vertical bone loss compared to socket filling without a membrane cover.

It can be speculated that the socket sealing material has the single function of remaining in situ long enough for the formation of granulation tissue underneath, which would cover the graft material inside the socket and give space for a keratinized mucosa after maturation. Despite this, the healing process of the oral mucosa is influenced by several factors, including transforming growth factor-beta (TGF-β), which demonstrated a capacity for tissue regeneration and the replacement of periodontal cells. Early proliferation of gingival fibroblasts, blood vessel formation, and extracellular matrix remodeling were related to TGF-β activity in a preclinical model,[47] suggesting its positive impact in periodontal healing. In vitro studies have shown that collagen membranes adsorb TGF-β from the environment, suggesting an intrinsic activity via TGF-β for soft and hard tissue regeneration.[48,49] Considering the similarity between the matrix and the membrane used in the present study, the authors believe that collagen matrices could also adsorb TGF-β locally, promoting tissue healing. Although the mechanisms of tissue regeneration are much more complex, the ability of collagen-based materials to adsorb TGF-β cannot be ignored. Studies that demonstrate this ability in collagen matrices are necessary, as well as studies that validate those hypotheses in a clinical scenario.

No clear relation could be established between the socket sealing approaches and the underlying hard tissue formation. The bone tissue was mostly immature, which is in line with other studies that showed a predominance of woven bone after 4 to 6 months of healing in alveolar sockets with bone fillers.[8,23,50] This delayed bone formation in sites with slowly reabsorbing biomaterials may partially explain the low insertion torque of dental implants (< 30 Ncm) in 55.5% of the patients (n = 12). It also opens space for speculation concerning the reasons for early implant failures, since all implant losses in this study occurred in immature bone with a large amount of nonmineralized matrix. It is noteworthy that the bone tissue sample of a patient who lost an implant was dominated by fibrous connective tissue. Therefore, a healing period of 4 to 6 months after alveolar ridge preservation seems to be insufficient to guarantee primary stability in dental implant placement due to the low bone tissue maturity. A human histologic study showed that 7 to 9 months after alveolar ridge preservation with xenografts was long enoughenough for lamellar bone formation.[31] Nevertheless, a systematic review detected no significant histologic difference between preserved sites and those submitted to spontaneous healing, and thus 3 to 4 months would be sufficient for implant placement.[51] Further research is needed to explain this puzzling issue.

Concerning clinical relevance, this research is a milestone for the decision-making of clinicians regarding the socket sealing materials for alveolar ridge preservation. No other study has assessed the tomographic and histologic aspects of socket sealing by comparing collagen matrices and membranes exposed to the oral cavity to autogenous soft tissue graft and untreated controls. Overall, the findings of this investigation indicate that collagen matrices, collagen membranes, and autogenous grafts have similar capacities to assist volumetric alveolar ridge preservation. However, xenogenous biomaterials do not increase postoperative morbidity because they do not require surgical access to a donor site. Clinicians should consider that using biomaterials adds costs to the treatment, and the decision to replace autogenous grafting techniques must be taken in consideration of the particularities of each case, according to the patient needs. Taken together,

the data of this research support and extend the existing knowledge of the use of socket sealing materials in alveolar ridge preservation procedures.

The present study has limitations that need to be acknowledged, and the reduced number of participants is probably the most significant. Despite the large volume of patients screened during the recruitment phase, the strict eligibility criteria, such as the need for intact alveolar walls in the preoperative period, excluded many individuals, which substantially affected the number of patients enrolled in the research. Moreover, the sample calculation a priori failed when the number of 10 participants per group was estimated, since a sample of approximately 240 patients was later calculated for this study. This quantity of individuals, however, is not feasible for a single-center clinical study. Therefore, it is recommended that upcoming studies consider using fewer experimental groups or follow a multicenter study format. In addition, linear and area measurements were employed for volumetric analysis of the alveolar ridge because they have a more applicable interpretation in the clinic. However, these parameters are surrogate endpoints to estimate the success of the treatment, and three-dimensional evaluations would provide more genuine information on the dimensional changes of the alveolar ridge. Thus, the findings of this research must be interpreted with caution.

Radiation protection should be a concern for future research. In the present study, two CBCT scans were necessary for data acquisition. An alternative approach could involve intraoral scanning to obtain a digitized surface mesh (eg, an STL [standard tessellation language] file) of the alveolar ridge before and after tooth extraction, avoiding radiation exposure. Furthermore, tomographic exams in the DICOM format can be overlapped on the scanning files, generating relevant data for assessing the tissue changes of hard and soft tissues. The employment of two layers of material to seal the socket seems to be a promising strategy for alveolar ridge preservation. Other studies have used two layers of collagen membrane,[45] a collagen membrane combined with a collagen matrix,[22] and a collagen membrane combined with an autogenous palatal flap.[34] Future randomized controlled clinical trials could verify the benefits of these approaches. Although the present research brings important information for the decision-making of clinicians about different strategies to seal the alveolar socket, the treatment outcomes should be centered on clinical endpoints such as the long-term survival of implants. Thus, the prospective monitoring of patients rehabilitated with dental implants after alveolar ridge preservation with different socket sealing approaches is recommended for further investigation.

CONCLUSION

Within the limitations of this study, socket sealing with a collagen matrix, a collagen membrane exposed to the oral cavity, or an autogenous soft tissue graft from the palate are suitable approaches for alveolar ridge preservation, showing no differences in terms of volumetric maintenance and tissue formation in a period of 4 to 6 months after tooth removal. The spontaneous healing of extraction sockets showed dimensional loss over time for the parameters of buccal bone height and cross-sectional alveolar ridge area. More studies with larger samples are necessary to confirm these observations.

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