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Randomised Controlled Trial
Pre-Implant Surgery

Synthetic polymeric barrier membrane associated with blood coagulum, human allograft, or bovine bone substitute for ridge preservation: a randomized, controlled, clinical and histological trial

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Abstract. During the normal healing process, an extraction site may lose significant bone volume, making implant placement problematic. Quantitative evaluations of the amount of bone maintained by socket preservation with various materials are limited. The objective of this study was to evaluate, both clinically and histologically, the extent of alveolar bone preservation by blood coagulum (BC) and the potential additional benefits of bone allograft material (AL) versus the state-of-the-art bovine bone mineral (BB), covered by a polyethylene glycol (PEG) barrier, in extraction socket grafting procedures. Adult patients ($n = 32$) with single-rooted teeth indicated for extraction were treated (45 sites). After atraumatic extraction, the sockets were filled with BC, AL, or BB and covered with a synthetic PEG barrier membrane. Changes in bone height and width were measured clinically and the amount of bone formed and residual graft particles were measured histologically after 6 months. Changes in ridge width at 6 months were −1.5 mm for AL versus −2.5 mm for BB and −2.3 mm for BC. New bone formation amounted to 47.8%, 33.3%, and 28.2% at BC-, AL-, and BB-treated sites, respectively. Using AL with the PEG barrier preserved the ridge width at 6 months better than BB or BC and resulted in similar amounts of bone histologically to BB.

Key words: tooth extraction; bone grafting; guided bone regeneration.

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Healing of an extraction socket is a complex biological process[1]. Alveolar bone structure is lost following tooth extraction, even in an intact extraction socket[2]. After healing, the buccal alveolar bone plate is located 1.9–2.2 mm apically compared with the height of the oral alveolar wall, due to continued tissue modeling of the alveolar bony walls[1]. The decrease in volume of tissues in the edentulous ridge, especially on the buccal side, results in a palatal/lingual shift of the residual bone crest[3–5]. These three-dimensional changes may result in difficulties in implant positioning and lead to aesthetic compromises in implant therapy[6]. Thus, technical refinements of tooth extraction and tissue reconstruction have been proposed in order to mitigate these deleterious biological events.

Several approaches have been evaluated to minimize hard and soft tissue alterations following tooth extractions and to preserve original ridge dimensions and contours, with special emphasis being given to ridge preservation procedures with intra-socket osseous grafts and/or membranes[7–15]. Among the biomaterials tested in ridge preservation procedures, deproteinized bovine bone mineral (BB) has been evaluated extensively[16–21]. However, this xenograft has an animal source and thus other materials have been investigated as alternatives, in particular allograft materials (AL), which have been tested extensively in regenerative alveolar grafting procedures[22–32].

A contemporary approach to the management of extraction socket defects with barrier membranes is the use of synthetic, absorbable barriers that can be custom-made intraoperatively for an individual defect[33]. More recently, a polyethylene glycol (PEG) hydrogel membrane has been tested in bone regeneration procedures with simultaneous endosseous titanium implant placement[34–36]. PEG hydrogels are highly biocompatible[37–40] and degrade by hydrolysis at 4–6 months after implantation[41,42]. A synthetic, degradable membrane composed of two liquid PEG compounds that react upon mixing and form a hydrogel has been developed, and this has demonstrated cell-occlusive properties[43] and prevention of soft tissue ingrowth[44]. Several experimental studies have demonstrated the bone regenerative potential of these membranes when employed in conjunction with a bone replacement graft in bony defects and for the treatment of dehiscence defects around implants[44–47]. None of these studies, however, evaluated this material without a bone graft in extraction defects.

The objective of this study was to evaluate, both clinically and histologically, the extent of alveolar bone preservation by blood coagulum (BC) and the potential additional benefits of AL versus the state-of-the-art BB, covered by a PEG barrier, in extraction socket grafting procedures.

Materials and methods

The study was designed as a randomized, prospective, parallel-arm, controlled clinical trial. It was conducted in accordance with the guidelines of the Declaration of Helsinki of 1975, as revised in 2000, and following approval by the Institutional Review Board of Boston University for research that involves human subjects. Written informed consent was obtained from all patients after they had been provided with a thorough explanation of the nature, risks, and benefits of the clinical investigation and associated procedures.

Study population and experimental design

Subjects were recruited from the patient pool of the Goldman School of Dental Medicine, Boston University (BUGSDM). Thirty-two adult patients with a total of 45 single-rooted teeth (incisor, canine, and premolar) indicated for extraction for periodontal, endodontic, or prosthetic reasons were included in the study. The extraction sites were distributed equally among the treatment groups (15 sites per group). Each extraction socket was filled with either blood coagulum, a mineralized ground cancellous human allograft graft material (AlloGraft, OCAN 250–1000 microns; Institut Straumann AG, Basel, Switzerland), or a bovine bone mineral (Bio-Oss, Geistlich Pharma AG, Wolhusen, Switzerland) and covered with a synthetic polymeric (PEG) barrier membrane (Institut Straumann AG). Smokers, patients with immunosuppressive systemic diseases (i.e., cancer, AIDS, diabetes), and patients with general contraindications for oral surgery were not included in the study.

Surgical procedure

Local anesthesia was obtained by means of regional blocks, followed by papillary intraseptal and palatal infiltration. Circumferential intrasulcular incisions were performed around the experimental teeth with a number 15C surgical blade. A buccal full-thickness envelope flap was elevated only if needed. The teeth were carefully luxated and extracted atraumatically. No fractures of the cortical plate occurred during the extraction procedures. The sockets were carefully curetted and irrigated with sterile saline solution. The sockets were then completely filled with either blood coagulum (BC group), the allograft material (AL group), or the bovine bone mineral (BB group). All sites were covered with a PEG liquid polymeric barrier (Figs 1–3).

The membrane is applied in a liquid state directly intraoperative using a syringe. It forms a hydrogel via a cross-

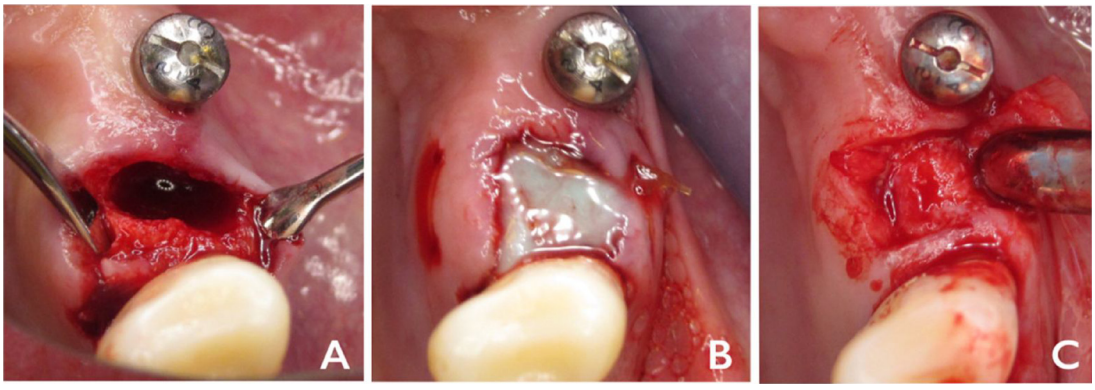

Fig. 1. Site treated with a PEG barrier and blood coagulum (BC): (A) extraction site, (B) PEG barrier in situ, (C) re-entry after 6 months.

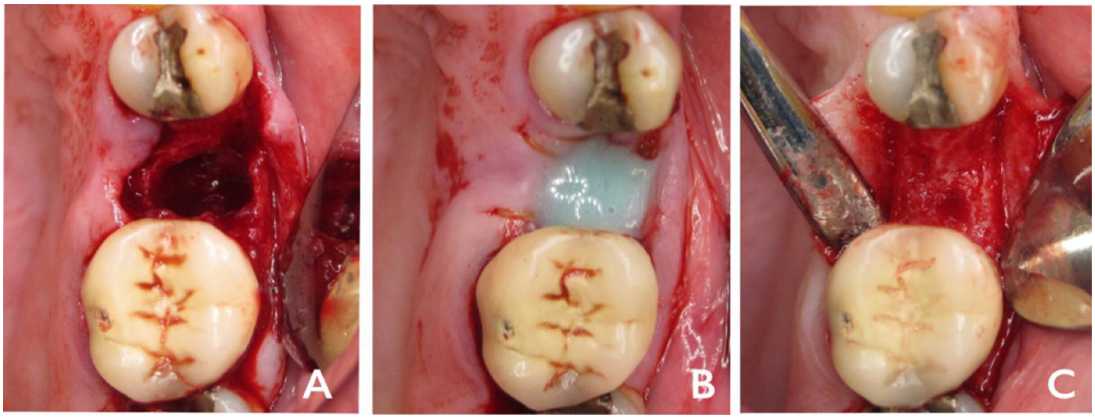

Fig. 2. Site treated with a PEG barrier and bone allograft (AL): (A) extraction site, (B) PEG barrier in situ over AL, (C) re-entry after 6 months.

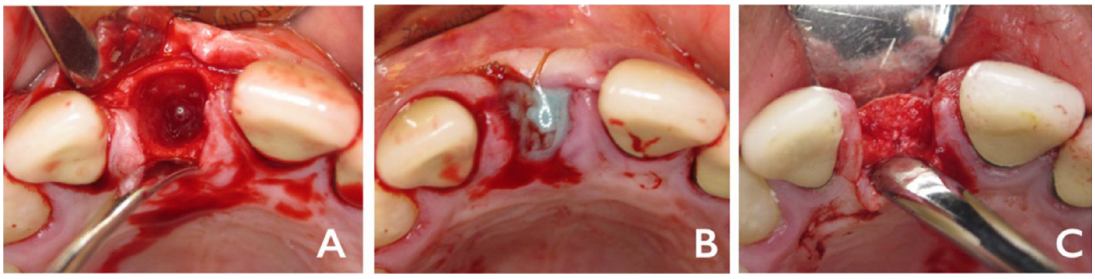

Fig. 3. Site treated with a PEG barrier and bovine xenograft (BB): (A) extraction site, (B) PEG barrier in situ over BB, (C) re-entry after 6 months.

linking reaction within approximately 90 s after application. Gelification is activated by the combination of PEG-A (containing acrylate as the terminal functional group), PEG-B (containing thiol as the terminal functional group), and activators A (viscosity modifier) and B (isotonic chemical solution creating an optimal pH to start the chemical reaction). The chemical components of PEG-A and PEG-B create a molecular network of PEG, which acts as a barrier and prevents the migration of soft tissue cells, while remaining permeable to nutritional substances. Biodegradation of the membrane occurs due to hydrolysis and this does not lead to any acidification of the surrounding tissues.

Flap stabilization and wound closure were obtained with internal horizontal mattress and single interrupted sutures.

Bone measurements

At the time of the surgery, just prior to graft placement, direct measurements were taken of the width of the bone crest, from the crest of the buccal bony wall to the crest of the palatal bony wall. This was done using a calibrated periodontal probe, at the point corresponding to the planned implant placement site, according to a customized acrylic surgical stent[25]. Diagnostic casts were made from alginate impressions to fabricate a surgical and clinical bone measurement assessment guide[48]. The crown of the non-restorable tooth was removed if present at implant placement, and four reference points were drilled through the template on the mid-buccal side of the alveolar bone crest using a carbide straight fissure bur. This clinical measurement guide indexed to the patient's dentition was used immediately after extraction to measure the existing bone level at the site. The mid-buccal vertical measurements were recorded to the nearest millimeter using a calibrated periodontal probe[25,26]. The same guide was used at the time of implant placement to measure the amount of bone regeneration after 6 months of healing[28] at the same sites from fixed landmarks, following full-thickness buccal and lingual/palatal flap elevation to expose the alveolar crest. The marginal bone levels were calculated as the distances between the coronal border of the measurement guide and the mid-buccal wall of the socket bone crest. The buccolingual width was measured as the distance between the most coronal portions of the buccal and the palatal–lingual bone crest in the middle of the socket with the aid of calipers[27,33].

All measurements were rounded to one decimal place. The difference in the measurements for all surgical sites after the tooth extraction and before the implant placement provided a clinical assessment of the amount of bone regeneration. Immediately after the bone measurements had been performed, a bone core was collected from the implant site with a 2.6-mm diameter trephine bur. The bone core was placed in 10% neutral buffered formalin within 5–10 min. Preparation of the implant site was then continued, in accordance with the manufacturer's instructions, for implant placement in the ideal prosthetic position, as determined with the surgical guide stent.

Histological procedures

Bone cores were taken at the time of implant placement, 6 months after the socket preservation procedure, using a trephine bur. Bone specimens were placed in neutral buffered saline immediately after harvesting. Within 24 h, samples were placed in 50% ethyl alcohol for transportation to the histology laboratory. Samples were demineralized in 10% ethy-

lenediaminetetraacetic acid (EDTA) in 0.1 M Tris buffer, rinsed in running water wash, dehydrated through a series of graded ethanol solutions, and embedded in paraffin. Paraffin blocks were trimmed with a microtome and every 10th section was mounted as a representative section and stained with hematoxylin and eosin. Histology slides were evaluated for quantitative analysis of vascular, marrow, trabecular, and graft particle architecture and histomorphometric analysis of mineralized bone (% area) and graft particles (% area). For the percentage area of mineralized bone, measurements were obtained from three slides for each region (apical, middle, and cervical third) and combined to calculate the arithmetic mean.

Perioperative and postoperative care

Provisional restorations were checked and adjusted to eliminate contact with the surgical area. Sutures were removed after 7 days and the wound cleaned carefully with sterile gauze soaked in saline, following which the field was evaluated. The patient was prescribed 0.12% chlorhexidine solution mouthwash for use twice daily as chemical bacterial plaque control. The patient was also instructed to use their routine plaque control regimen, except in the operated area.

Statistical analyses

The primary outcomes of this study were (1) alveolar bone height loss, (2) alveolar bone width loss, and (3) mean percentage area of mineralized bone. Summary statistics (mean, standard deviation, median, minimum, and maximum values) were calculated for all endpoints in each experimental group. For the secondary analysis, one-way analysis of variance (ANOVA) was used to detect group differences. Post-hoc multiple comparisons were made using the Bonferroni and Holm test. Statistical significance was set at the 95% probability level ($P < 0.05$).

Results

Thirty-two patients (14 male, 18 female), ranging in age from 34 to 52 years (mean ± standard deviation age 42 ± 8 years), were treated. At the 6-month evaluation, 14 BC sites, 13 AL sites, and 14 BB sites were analyzed (Table 1); four sites were discarded due to patient drop-out or inadequate sampling for histological evaluation. No exfoliation of graft material during healing was observed clinically, nor was this reported by the patients for any site. No signs of erythema, edema, swelling, or suppuration were noticed in the soft tissues of any of the patients. Post-surgical complications were minimal for all treatment modalities tested.

Table 1. Distribution of the extraction sockets among the study groups.

Group	Maxillary			Mandibular			Total
	Premolar	Canine	Incisor	Premolar	Canine	Incisor	
BC	7	0	4	2	0	1	14
AL	4	1	4	3	1	0	13
BB	3	3	4	3	1	0	14
Total	14	4	12	8	2	1	41

BC, blood coagulum + PEG membrane; AL, bone allograft + PEG membrane; BB, bovine bone + PEG membrane.

Changes in bone height are presented in Table 2 and Figs 4 and 5. There were no significant differences among the groups with regard to the baseline measurements of the ridge height at the buccal, palatal/lingual, and central aspects of the extraction sockets. Intra-group repeated measurements obtained at 6 months after tooth extraction showed that bone height was not significantly different to baseline at the buccal aspect or the lingual aspect for all of the groups, demonstrating that the three treatments were equally effective in limiting buccal and lingual crest bone loss. Significant vertical bone gain was detected 6 months after treatment in comparison with baseline measurements at the central aspect of the socket for all groups (all $P < 0.01$), indicating that significant bone fill had occurred. No differences in vertical bone gain at the central aspect were detected between the BB, AL, and BC groups after 6 months ($P = 0.77$), demonstrating that the treatments provided were equally effective in promoting vertical bone regeneration in extraction socket defects. No inter-group differences were observed for measurements obtained at baseline and after 6 months at the lingual aspect of the sockets, thus, as noted for the buccal aspect, all treatments were also equally effective in limiting lingual crest bone loss.

Changes in bone crest width are presented in Table 2 and Fig. 6. Baseline measurements of the ridge dimensions revealed a mean of 9.5 ± 1.2 mm for the BC group and 9.0 ± 1.6 mm and 9.5 ± 1.2 mm for the AL and BB groups, respectively ($P = 0.61$). Thus, at baseline the widths of the alveolus were similar in the three groups. After 6 months of healing, horizontal bone loss varied between −1.5 ± 1.9 mm (15.0%) for AL and −2.5 ± 1.6 mm (25.9%) for BB in conjunction with PEG barriers (Fig. 6A shows the changes in millimeters and Fig. 6B shows the percentage changes). The AL group did not exhibit a significant change in ridge width from baseline ($P = 0.30$), demonstrating that AL was effective in limiting horizontal bone loss. Horizontal measurements were significantly reduced after 6 months in the BC and BB groups in comparison with baseline (both $P < 0.01$). Therefore, in conjunction with a PEG barrier, AL appears to be more effective than BC and BB in preventing horizontal bone loss following tooth extraction. The repeated measurements obtained after 6 months showed that the AL group exhibited less buccopalatal change in bone width in comparison with the BB group (73% less) and the BC group (59% less). The difference between the BB group and BC group was not significant ($P = 0.43$), demonstrating that BB was as efficient as BC in preserving ridge crest width.

Histological and histomorphometric data are presented in Fig. 7 and Fig. 8, respectively. A total of 35 samples were collected and found to be adequate for histological processing and evaluation at 6 months (9 BC, 13 BB, 13 AL). BC and AL were equally effective in promoting bone regeneration in the alveolar extraction defects, since the difference in new bone formation between these groups was not statistically significant ($P = 0.12$). Surprisingly, the BB group exhibited significantly less regenerated bone than the BC group ($P = 0.02$). The AL group exhibited approximately 0.7% less residual graft particles than the BB group. However, the difference in the amount of residual graft material between the AL group and the BB group (8.2% vs. 8.9%, respectively) was not statistically significant (ANOVA, $P = 0.08$). Similarly, there was no significant difference in the amounts of mineralized tissue (vital bone + graft particles) between the BB (37.1%), AL (41.6%), and BC (47.8%) groups at 6 months after extraction (Fig. 8).

Discussion

This study was designed to evaluate, clinically and histologically, the extent of

Table 2. Intraoperative clinical measurements (in millimeters) obtained at baseline and after 6 months of healing; mean ± standard deviation values.

	Buccal height (mm)			Lingual height (mm)			Central height (mm)			Width (mm)		
	Baseline	6 months	*P*-value	Baseline	6 months	*P*-value	Baseline	6 months	*P*-value	Baseline	6 months	*P*-value
BC	11.79 ± 2.55	11.71 ± 2.30	0.89	10.14 ± 2.14	10.79 ± 2.26	0.89	21.07 ± 2.59	11.14 ± 2.44	<0.01	9.50 ± 1.16	7.21 ± 1.97	<0.01
AL	12.00 ± 3.02	12.38 ± 2.43	0.89	10.15 ± 2.37	10.92 ± 2.56	0.89	22.23 ± 2.52	11.69 ± 2.86	<0.01	9.00 ± 1.63	7.54 ± 1.90	0.30
BB	11.85 ± 2.82	12.08 ± 2.72	0.89	10.46 ± 1.50	11.23 ± 2.25	0.89	23.69 ± 3.31	11.31 ± 3.19	<0.01	9.54 ± 1.15	6.86 ± 1.29	<0.01
P-value	0.89	0.89		0.89	0.89		0.25	0.77		0.61	0.60	

BC, blood coagulum + PEG membrane; AL, bone allograft + PEG membrane; BB, bovine bone + PEG membrane. *P*-value = significance level.

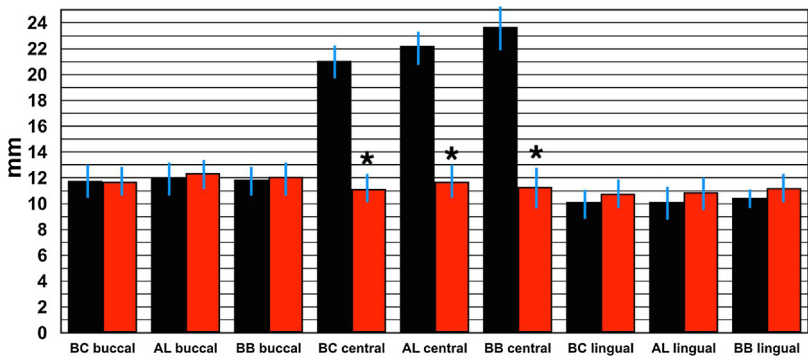

Fig. 4. Mean measurements of bone height (in millimeters) obtained at baseline (black bars) and after 6 months (red bars); standard deviations are shown as blue bars. BC: blood coagulum + PEG membrane; AL: bone allograft + PEG membrane; BB: bovine bone + PEG membrane. *$P < 0.01$ vs. baseline.

alveolar bone preservation of blood coagulum and the potential additional benefits of simultaneous grafting procedures for bone regeneration in human extraction socket defects covered by a PEG barrier. The results showed that the three treatment procedures tested were similarly effective in preserving the ridge dimension and in regenerating bone in these defects. This suggests that an in situ polymerizing barrier membrane used alone, or in conjunction with a bone replacement graft, demonstrates adequate clinical performance in bone regenerative therapy for socket preservation procedures in humans.

The results of this study compare favorably with those of previous reports in relation to the potential for preservation of the alveolar ridge dimensions following tooth extraction. A recent meta-analysis by Tan et al.[48], reported that human reentry studies showed horizontal bone loss of 3.79 ± 0.23 mm (29–63% of the original alveolar width) and vertical bone loss of 1.24 ± 0.11 mm at buccal sites (11–22% of the original alveolar height) at 6 months following tooth extraction, followed by gradual reductions in dimensions thereafter. The present study found a much reduced bone loss for all treatments tested. Horizontal bone loss varied between −1.5 ± 1.9 (15.0%) for AL and −2.5 ± 1.6 (25.9%) for BB in conjunction with PEG barriers (Fig. 6). Interestingly, the mean percentage of horizontal bone loss in the AL group appears to be about half that of the lowest value documented for other therapies by Tan et al.[48]. However, buccal bone remodeling amounted to a slight gain 0.07 ± 1.33 in the BC group and a slight loss of −0.39 ± 1.27 mm in the AL group in conjunction with the PEG barrier. Thus, it appears that treatment with the PEG membrane alone resulted in the smallest amount of buccal vertical crest reduction and that AL resulted in the best preservation of ridge width.

The data presented here demonstrate that the PEG barrier membrane was effective in promoting bone formation in human extraction socket defects. Interestingly, the largest amount of regenerated bone (47.8 ± 0.1%) was detected histologically when the barrier membrane

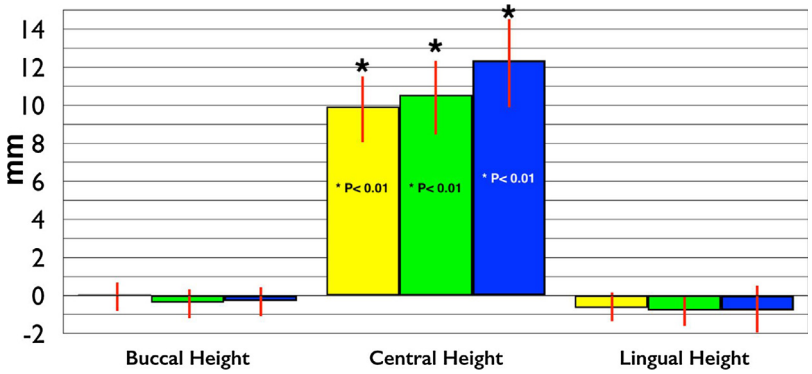

Fig. 5. Mean changes in bone height measurements from baseline to 6 months of healing (in millimeters); standard deviations are shown as red bars. Yellow bars: BC (blood coagulum + PEG membrane); green bars: AL (bone allograft + PEG membrane); blue bars: BB (bovine bone + PEG membrane). *$P < 0.01$ vs. baseline.

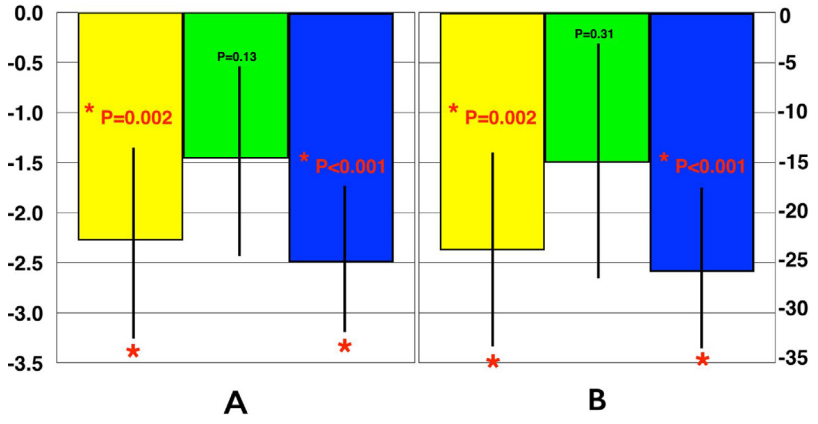

Fig. 6. Mean changes in bone width measurements from baseline to 6 months: (A) changes in millimeters (mm), and (B) changes as percentages (%) from the original ridge width at the time of extraction; standard deviations are shown as black bars. Yellow bars: BC (blood coagulum + PEG membrane); green bars: AL (bone allograft + PEG membrane); blue bars: BB (bovine bone + PEG membrane). *$P < 0.01$ vs. baseline.

was used alone. This finding is in accordance with a recent animal study, which also found no significant enhancement in bone regeneration when the barrier was employed in conjunction with a synthetic bone graft, leading to speculation about a possible osteoconductive potential of the membrane[49]. Few studies have evaluated histologically the healing after the use of membrane alone in the treatment of extraction socket defects[18,50]. Carmagnola et al. compared the outcomes of collagen membrane alone or in conjunction with bovine bone mineral and observed significantly more bone in the membrane alone group (40.1% vs. 26%, respectively)[18]. Luczyszyn et al. compared an acellular dermal matrix alone or in conjunction with absorbable hydroxyapatite and also found better results with the barrier alone (46% vs. 1%, respectively)[50]. Both studies are in agreement with the current study results.

The effects of allografts in membrane-treated extraction socket defects have been documented previously[10,22]. Smukler et al. evaluated decalcified freeze-dried bone allografts (DFDBA) in conjunction with non-absorbable barriers (expanded polytetrafluoroethylene (ePTFE)) over a healing period of 8–23 months and found approximately 56% new bone and 2.5–8.7% residual graft particles[22], while Iasella et al. evaluated freeze-dried bone allografts (FDBA) in conjunction with absorbable collagen barriers over a healing period of 4–6 months and found 28 ± 14% new bone and 37 ± 18% residual graft particles[10]. The present data demonstrated more bone than Iasella et al.[10] and less than Smukler et al.[22]; this possibly reflects differences in study design, such as defect types and possibly healing times. The higher amounts of bone observed in the study by Smukler et al.[22] are possibly the result of the continued

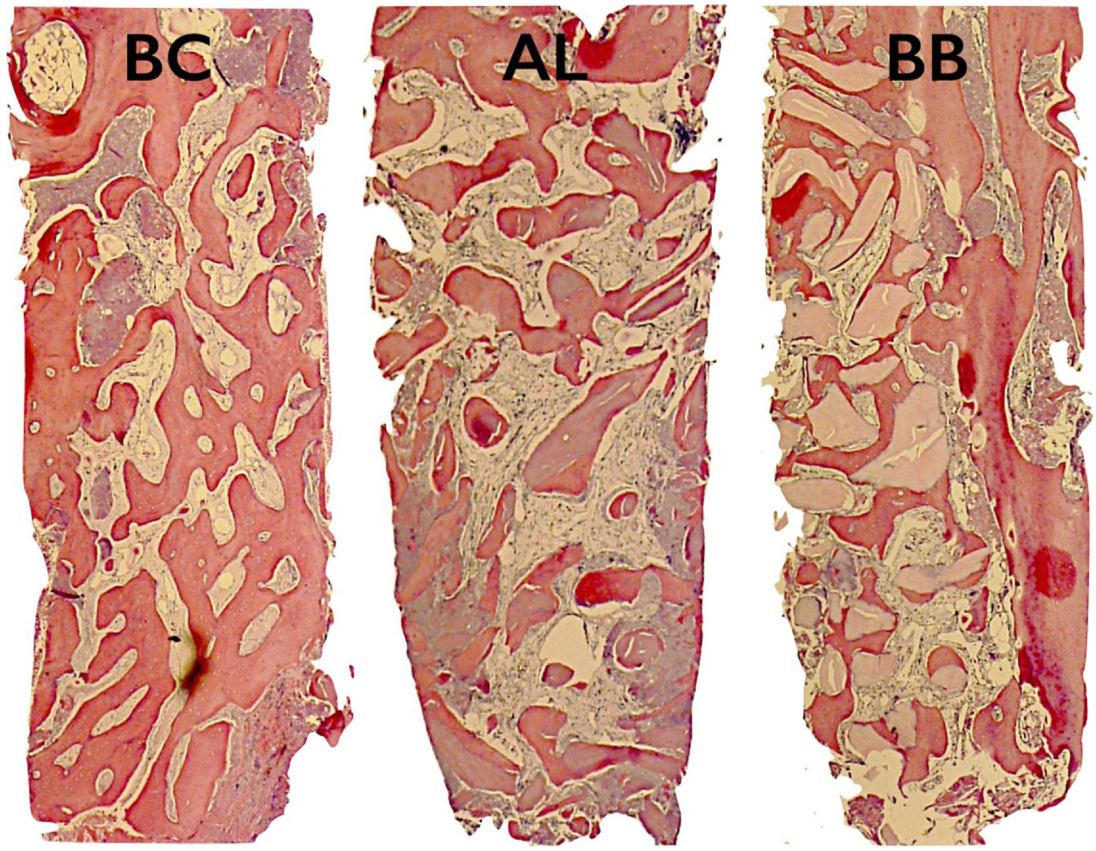

Fig. 7. Histological evaluation of sites treated with blood coagulum (BC), bone allograft (AL), and bovine bone (BB) at 6 months of healing; hematoxylin and eosin stain, magnification ×20.

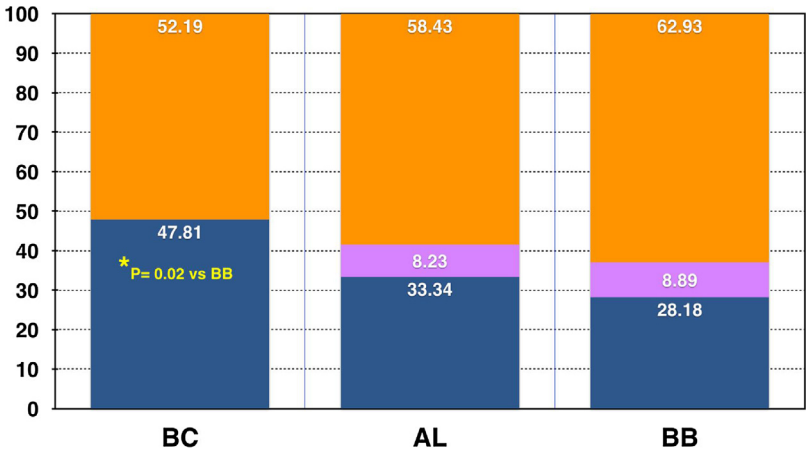

Fig. 8. Histomorphometric measurements of biopsies obtained after 6 months of healing (data presented as percentages). The amounts of new bone are depicted in blue, residual graft particles in purple, and connective tissue in orange. BC: blood coagulum + PEG membrane; AL: bone allograft + PEG membrane; BB: bovine bone + PEG membrane group. **P* = 0.02 vs. BB.

'creeping-substitution' phenomenon observed through a longer healing time. The similar, albeit smaller, amounts of bone found in the study by Iasella et al.[10] may reflect the similar healing times of the present and the latter study and also the enhanced healing capacity of PEG as compared to collagen barriers[51] or plugs[52]. PEG has been shown to increase the area of regenerated bone to a greater extent than collagen membrane[51]. The amount of residual graft particles found in the present study was very similar to that reported by Smukler et al.[22], but clearly much less than found by Iasella et al.[10]. This may indicate an increased resorption of the graft particles when combined with a PEG barrier, as noted in other previous studies[45–47].

Several studies have evaluated the effects of bovine bone mineral in extraction socket defects treated with absorbable collagen membranes[18–21,53–56], and have reported new bone varying from 5.3% to 40.8%[53,55] and residual particles varying from 16% to 25%[20,21]. Thus, the results of the present study appear to be within the range reported previously for new bone, however with much less residual graft particles. Interestingly, most studies had healing periods of 4–7 months and exhibited between 5.3% and 32.8% new bone[18–21,53–55]. An exception is the study by Perelman-Karmon et al., which lasted 9 months and exhibited significantly more new bone (40.8 ± 10.7%)[55]. Again, the present study data appear to indicate an increased resorption of bovine bone mineral particles when combined with a PEG barrier[44–47,51]. Moreover, the data from this extraction socket model also appear to corroborate the finding of a previous study that a PEG barrier membrane is comparable to a standard collagen membrane in the treatment of bony dehiscence defects around dental implants[36].

Several measurement techniques have been used to determine the dimensional changes in the alveolar ridge in clinical studies, including direct measurements, two-dimensional radiographs (peri-apical and panoramic radiographs), three-dimensional radiographic evaluations, and study casts[57]. In evaluating the present study data, it is important to recognize that the measurement method employed (periodontal probe) may not be the most advanced, especially when compared to optical scanning and/or cone beam computed tomography (CBCT)[57–62]. However, both direct intraoperative measurements during re-entry surgery and three-dimensional radiographic evaluation of the hard tissues are recommended for accurate estimation of the changes in alveolar ridge dimensions following tooth extraction[62], since it appears that direct clinical intraoperative measurements and CBCT measurements are largely consistent in the evaluation of the alveolar bone height and width after alveolar ridge preservation procedures[63].

Within the limitations of this study, it is concluded that the PEG barrier is an effective device for alveolar ridge preservation in humans when used in conjunction with blood coagulum, allograft material, or bovine bone mineral. The combined use of allograft material and a PEG barrier post extraction preserves the ridge width significantly better than a PEG barrier in conjunction with blood coagulum or bovine bone mineral. All three treatments performed equally well histologically and resulted in similar amounts of mineralized tissue formation at 6 months after treatment.

Funding

None.

Competing interests

The authors do not have any financial relationships that may pose a conflict of interest or potential conflict of interest and have no commercial relationships with regard to any of the products or instruments employed.

Ethical approval

The Institutional Review Board of Boston University approved the study (protocol number H-31436).

Patient consent

Not required.

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