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ORIGINAL ARTICLE

Radiographic evaluation of a novel bone adhesive for maintenance of crestal bone around implants in canine oversized osteotomies

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Abstract

Background: A novel bone adhesive (tetracalcium phosphate and O-phospho-L-serine) has been developed as an osteoconductive, biodegradable bone-adherent material. The purpose of this study was to evaluate the maintenance of crestal bone/material level by standardized radiographs.

Methods: This was a randomized, controlled, three arm, prospective study. Twenty-six mixed breed hound dogs were included in this study. Three implants were placed on either side of the mandible with either bone adhesive (BA), bovine bone mineral (BBM), or no biomaterial (negative control [NC]). Standardized periapical radiographs were taken immediately after implant placement and at every month up to 1 year. The vertical distance between the implant platform to the first radiopaque material on both the mesial and distal surfaces were measured and crestal bone/material level changes were analyzed.

Results: The crestal bone/material level adjacent to BA was stable and maintained throughout the study. There were statistically significant differences found between BA and NC in terms of maintenance of crestal bone levels at any given timepoint.

Conclusion: This study demonstrated that BA maintained crestal bone levels and had a similar ability to maintain that level over 1 year compared with BBM.

KEYWORDS
dental cements, dental implantation, endosseous, dental implants, mandible, minerals, osseointegration

1 | INTRODUCTION

After endosseous cylindrical dental implants were introduced to the field of dentistry,[1] they have become a major treatment option to replace missing teeth. Since then, numerous efforts have been made to accelerate the osseointegration process and to shorten the treatment period.[2] By modifying the implant surface texture from a machined surface to a roughened surface, clinicians were able to load the implant 6 to 8 weeks from the surgical placement instead of waiting for 3 to 6 months.[3,4] Placing immediate implants is another way to dramatically shorten the treatment period by placing the implant in fresh extraction sockets rather than waiting to place them in a well healed ridge.[5] A classification system for the timing of implant placement after tooth extraction has been proposed at the Third International Team for Implantology Consensus Conference.[6] Type 1 placement refers to

immediate placement where the implant is placed on the day of tooth extraction without healing of the bone and soft tissue. Type 2 placement refers to early placement after soft tissue healing (typically 4 to 8 weeks of healing) where the implant is placed in a post-extraction site with increased soft tissue volume but without significant bone healing. Type 3 placement refers to early placement with partial bone healing (typically 12 to 16 weeks of healing) where the implant is placed in a post-extraction socket with healed soft tissue and significant bone healing. Type 4 placement refers to late placement (typically >16 weeks of healing) where the implant is placed in a fully healed socket.

There are several advantages for immediate implant Type 1 placement. First, it allows for a reduced number of surgeries as well as the overall treatment time.[7] Moreover, it is thought to be beneficial for increased bone preservation and more optimal esthetics of the soft tissues particularly in the maxillary anterior esthetic zone.[8] However, there are some challenges related to this protocol. One of the most critical problems is the potential lack of stability due to the discrepancy between the implant diameter and the extraction socket. Achieving stability during healing for endosseous implants is an absolute requirement for osseointegration.[9] Excessive movement at the initial healing stage promotes a fibrous encapsulation around the implant rather than bone formation leading to failure of osseointegration.[10] To obtain primary stability for immediate implants, the following techniques have been proposed including placing longer implants to engage the apical bone beyond the extraction socket, offsetting the osteotomy from the original tooth angulation buccally/lingually to engage more native bone, and using a wider diameter implant to engage the socket walls.[11] However, none of these procedures create immediate primary stability unless native bone is engaged and there are inherent problems related to these techniques such as; undesirable implant angulation and locations leading to restorative complications, limitations of the anatomical structures that prevent a longer or wider implant, and predisposing bone loss and implant exposure.[12] Therefore, there is a significant desire for a technique that will facilitate instant stabilization of the immediate Type 1 implant and will allow the placement of the implant in restoratively and surgically driven positions within the original extraction socket.

Bioresorbable BAs[13–17] are potential candidates to be used for immediate stabilization of the dental implant. Calcium phosphate bone cements have good biocompatibility and capacity for promoting osseoconduction and osseointegration.[18–25] They are normally provided in a solid and liquid form. When they are mixed together, it turns into a paste that progressively sets and hardens into a solid mass through a dissolution and precipitation process.[26] Tetracalcium phosphate is the most common material among the calcium phosphates[27] and is widely used in the medical field. However, one of the biggest challenges, particularly for intraoral use, is to form a bond to the bone in a wet environment that is both strong enough to bear clinical loading and sustainable enough to allow new bone formation. To overcome this problem, the addition of non-collagenous bone matrix proteins were advocated. They are known to play an important role in mineral nucleation and osteogenic differentiation.[28] Phosphorylated amino acid residues such as O-phospho-L-serine are thought to be responsible for inducing the nucleation of hydroxyapatite, resulting in enhanced bone formation.[29,30] Moreover, O-phospho-L-serine is a key component of the proteinaceous glue that is effective under water and enhances the adhesive property of tetracalcium phosphate under a wet environment.[31,32] The combination of tetracalcium phosphate and O-phospho-L-serine created a novel BA.[27] In a previous publication, Cochran et al. reported that this novel BA demonstrated a 20 Ncm reverse torque value at 24 hours from implant placement and 40 Ncm reverse torque value at 10 days post-implant placement and proved that the effectiveness of this material as an immediate stabilizer of loose dental implants.[33]

Maintenance of crestal bone level is an important factor for the successful implant therapy and radiographic evaluation is an important measure to assess any material placed around dental implant.[34] However, there is no study up to date that evaluated the crestal bone level stability around the implant stabilized by this novel BA. The purpose of this study was to evaluate the radiographic marginal bone/material levels around implants placed in oversized osteotomy sites with this novel BA compared with a control and bone graft in a canine model.

2 | MATERIALS AND METHODS

2.1 | Study materials

This was a randomized, controlled, three arm, prospective study. The test material, a novel bone adhesive (BA)[1] used in this study consisted of 61.5% tetracalcium phosphate and 38.5% phosphoserine mixed with water and enclosed in a two-chamber plastic capsule. One arm received commercially available bovine bone mineral (BBM)[2] and another arm received no bone grafting material (blood clot only) served as a negative control (NC) with implant placement.

[1] Tetranite Stabilization Material, RevBio, Boston, MA
[2] Bio-Oss, Geistlich Pharma, Princeton, NJ

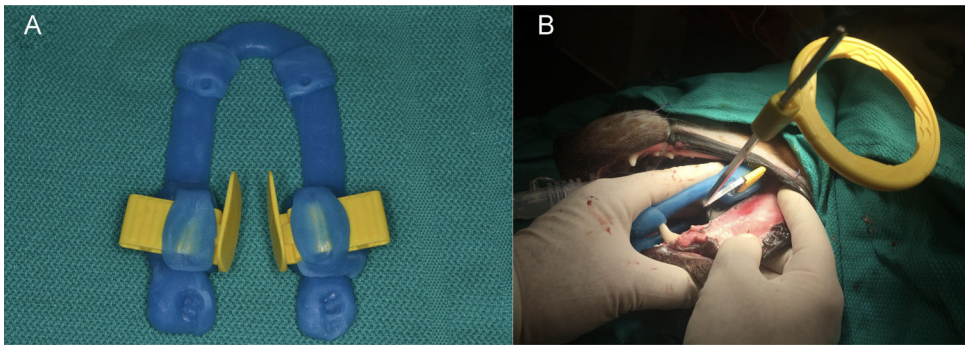

FIGURE 1 **A**) Radiographic stents were fabricated for standardized radiographs using a light cured acrylic resin material. **B**) The stent was used to take a standardized radiograph

2.2 | Study animals

Twenty-six healthy, mixed breed hound dogs were included in this study. The animals were all at least 1-year-old and weighed >25 kg at the time of implant placement. These animals were randomly assigned to a 1-day, 10-day, 3-week, 4-month, 9-month, and 12-month cohort group depending upon the timing of their necropsy after implant placement. Five animals were enrolled in each of the 1-day, 10-day, 4-month, 9-month, and 12-month cohorts. One animal was enrolled in a 3-week cohort. This study was approved by the institutional animal care and use committee (20170159AR).

2.3 | Surgeries–extraction

The surgical field was disinfected with 7.5% povidone-iodine solution. After administering local anesthesia using 2% lidocaine with 1:100,000 epinephrine, full thickness mucoperiosteal flaps were reflected. The teeth were sectioned with a disk and extraction of the mandibular second, third, and fourth premolars and first molars were performed bilaterally under general anesthesia as atraumatically as possible. Alveoloplasty was completed to eliminate any bony irregularities. The flaps were reapproximated and sutured with 4-0 polytetrafluoroethylene sutures.

2.4 | Fabrication of radiographic stent

The surgical sites were allowed to heal for at least 12 weeks. During that period, radiographic stents were fabricated for standardized radiographs using a light-cured acrylic resin material. Film-holding bite blocks with a paralleling beam-guiding device[3] were adapted to the light-cured acrylic resin engaging only the canines and the second molar teeth (Figs. 1A and 1B).

2.5 | Surgeries–implant placement and administration of study materials

Three implants were placed on either side of the mandible with BA, BBM, or no bone grafting material (NC). Before the surgery, randomization was performed to allocate BA and BBM so that they were equally placed in either the anterior or posterior sites without bias. The surgical field was disinfected with 7.5% povidone-iodine solution. Any calculus on the surface of the teeth was removed with hand scaler. After administration of local anesthesia using 2% lidocaine with 1:100,000 epinephrine, full thickness mucoperiosteal flaps were reflected. Alveoloplasty was performed to establish a flat table that was 6-mm wide in a bucco-lingual dimension and perpendicular to the long axis of the planned implants. A ø1.8-mm round bur was used to mark the center of the osteotomy. The posterior osteotomy site was located 6 mm from the mesial surface of the second molar. From that point, middle and anterior osteotomies were prepared to provide a 12 mm distance between each osteotomy site; ø2.2 and ø2.8 mm pilot drills were used to prepare the osteotomies to 8 mm in depth for all sites (850 rpm). Then, the posterior osteotomy was completed by the following drill sequence; ø3.5-mm twist drill, ø4.2-mm twist drill, and latch reamers[4] with ø4.5, ø5.0, and ø5.5 mm by 6 mm in depth. This drill sequence allowed the operator to consistently create a standardized osteotomy as shown in Figures 2A and 2B. With this osteotomy design, the implant engaged only the apical 2 mm in the native bone and therefore lacked stability. After the completion of the osteotomies, either BA or BBM was administered in the posterior site depending upon the randomization scheme. During the administration of the materials, direction indicators were placed in the middle osteotomy site to avoid any contamination of that site and to provide for alignment of the implants. Cover screws were placed on the implants and the hand

[3] Rinn-XCP posterior, Dentsply Sirona, York, PA

[4] Latch reamers, Bicon, Boston, MA

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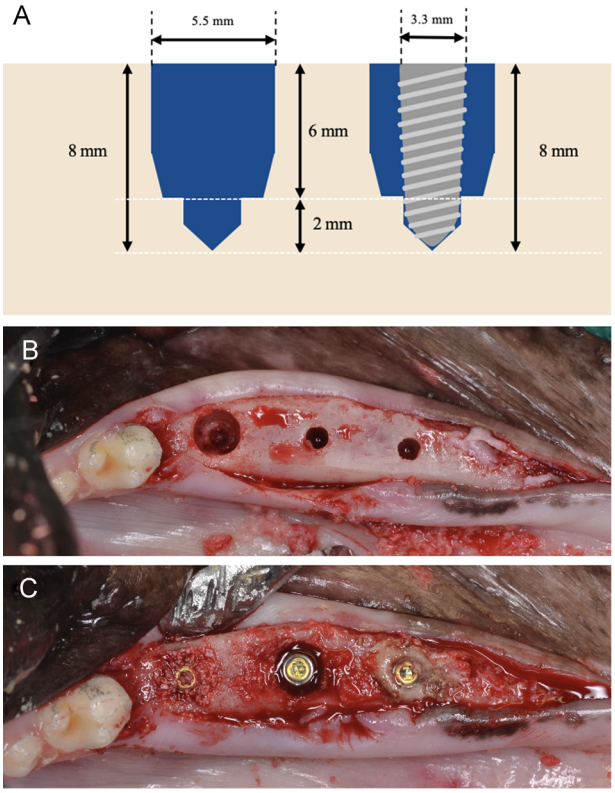

FIGURE 2 **A**) Design of the osteotomy used in this study. **B**) A completed oversized osteotomy is shown in the posterior position (left most site next to the tooth). The middle site and site on the right of the photo have been prepared for the implant diameter but not been oversized (widened) when the photo was taken. **C**) Anterior site (to the right of the photo) received BA, the middle site received no biomaterial (NC), and the posterior site (to the left of the photo beside the tooth) received BBM

driver was engaged in the cover screw as the implant carrier. The implants were placed into the osteotomy by hand. For the administration of BA, BA was activated in its sterile package and then triturated for 12 seconds. The mixed capsule was then transferred to the sterile dispensing applicator. BA was then injected directly into the osteotomy site. After 30 seconds, the implant was placed using the hand driver into the osteotomy site with slow rotational movement of one clockwise full rotation to engage the apical 2 mm of bone. The implant was stabilized using the operator's hand for 4 minutes from the initial mixing and then allowed to set chemically for a total of 10 minutes from the initial mixing. Any excess material was trimmed to the level of the alveolar crest of the ridge using a hand instrument after the material was completely set. For BBM, after the implant placement, the material was hydrated with saline for 3 to 5 minutes and gently packed into the space surrounding the implant to the level of the alveolar crest. For NC, the implant was placed with the hand driver into the osteotomy site without the addition

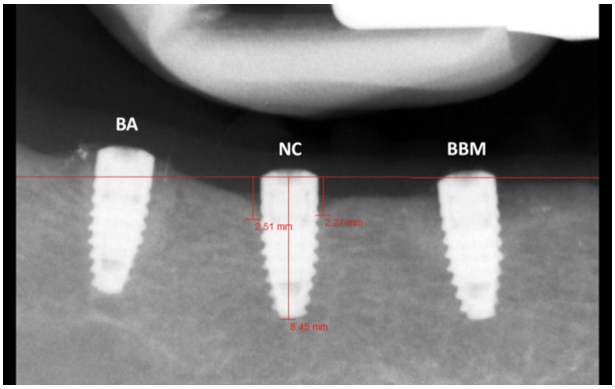

FIGURE 3 An example of standardized radiograph used for the radiographic analysis. Measurements were made as shown in the image (the middle implant). Implant length was measured in the image and was compared to the actual implant length reported by the manufacturer to account for the distortion of the image

of any bone grafting material (Fig. 2C); 4-0 dense polytetrafluoroethylene sutures were then used to close the surgical site. Primary closure was achieved to submerge all the implants.

2.6 | Radiographic analysis

Periapical radiographs (PAs) were taken immediately after implant placement and at every month until necropsy was performed (Fig. 3). For all canines, an attempt was made to standardize the PAs by using a custom-made radiographic stent. However, in some cases, since the custom-made radiographic stent was unable to capture the apex of the implant, non-customized radiographic holders were then used to take the PAs until the custom stent could be adjusted. All PAs were assigned a random code allowing a masked evaluation in regard to the time point and the material used for each specific surgical site. One examiner evaluated the whole series of PAs (RS); 15% of the PAs were evaluated for the calculation of intra- and inter-examiner error (RS, AJ) as described in the statistical analysis section. A digital medical imaging software[5] was used to analyze each PA. On each PA, the vertical distance between implant platform to the first radiopaque material on both the mesial and distal surfaces were measured. All the measurements were calibrated based on the implant length shown on the PA referring to the true implant length given by the manufacturer.

[5] MiPACS Dental Enterprise Viewer, Medicor Imaging, Charlotte, NC

2.7 | Histologic evaluation

After a euthanasia of the canines, an oscillating autopsy saw was used to harvest both left and right hemimandibles. Excised hemimandibles assigned for histologic evaluation were then placed in 10% neutral buffered formalin. The ground-section slides were created and stained with Stevenel blue and Van Gieson picro fuchsin for histologic analysis.

2.8 | Statistical analysis

Summary statistics are presented as means with SEs of measurements (mean ± SD). To detect intergroup differences at each timepoint, ANOVA models were implemented followed by Tukey multiple comparisons post-hoc tests for pairwise comparisons when indicated. The consistency of intra- and inter-examiner agreement for the radiographic measurements was assessed via the intraclass correlation coefficient (ICC). Two-way mixed-effect models were implemented in STATA statistical software to calculate the ICCs.

2.9 | Power analysis

For sample size estimation a clinically relevant difference of 1 mm in radiographic bone level between BA and NC with an 80% power was considered using unpaired post-hoc test with Tukey adjusted alpha levels($\alpha = 0.017$), which indicated an effective sample size of N = 22 implants per group, that is, 11 dogs with two implants per group in each dog (six implants per dog). After adjusting for a 25% attrition rate due to possible complications and/or implant failures the effective sample size at the 4-month primary end point was N = 30 implants per group, that is, 15 dogs with two implants per group in each dog, which exceed the minimum requirement.

3 | RESULTS

All experimental dogs survived until their designated necropsy date and no adverse systemic complication was observed. One dog lost two implants in BA sites and caused significant deviation for the radiographic analysis due to the inability to measure the platform to the first radiopaque material. Therefore, that dog was excluded from the radiographic analysis. The primary outcome measure in this study was to radiographically measure the marginal bone/material level change. Intra-examiner agreement for this outcome ranged from moderate (ICC = 59%) to excellent (ICC = 98%)[35] depending on the intraoral site with the least consistency in mesial aspects of anterior implants possibly owing to radiographic angulation. Similarly, inter-examiner reliability ranged from moderate (ICC = 56%) to excellent (ICC = 93%). In all cases when inter-examiner differences exceeded 1 mm (3% of the radiographic images that were measured) the radiographs were also assessed by a third gold standard examiner (CD) whose results were considered definitive and used in the analyses.

TABLE 1 Result of radiographic analysis

Time	BA	BBM	NC
Implant placement	0.291 ± 0.29**	−0.182 ± 1.20**	−4.321 ± 1.20
Week 2	0.246 ± 0.25**	0.205 ± 0.64**	−3.316 ± 1.66
Week 4	0.290 ± 0.31*	0.293 ± 0.49*	−1.384 ± 1.39
Week 8	0.364 ± 0.29*	0.251 ± 0.48*	−0.376 ± 0.69
Week 12	0.335 ± 0.29*	0.179 ± 0.51*	−0.381 ± 0.57
Week 16	0.356 ± 0.29*	0.144 ± 0.55	−0.381 ± 0.59
Week 20	0.273 ± 0.26*	0.262 ± 0.57	−0.289 ± 0.56
Week 24	0.328 ± 0.26*	0.196 ± 0.53	−0.304 ± 0.57
Week 28	0.346 ± 0.22*	0.208 ± 0.54	−0.358 ± 0.53
Week 32	0.320 ± 0.25*	0.250 ± 0.57	−0.250 ± 0.37
Week 36	0.293 ± 0.24*	0.209 ± 0.49	−0.280 ± 0.36
Week 40	0.394 ± 0.25*	0.374 ± 0.58	−0.410 ± 0.31
Week 44	0.406 ± 0.25*	0.398 ± 0.56	−0.412 ± 0.31
Week 48	0.396 ± 0.26*	0.376 ± 0.58	−0.450 ± 0.32
Week 52	0.390 ± 0.23*	0.370 ± 0.59	−0.468 ± 0.38

BA, bone adhesive; BBM, bovine bone mineral; NC, negative control (no biomaterial).

Mean values ± SD (mm) as measured from the most coronal portion of the platform to the first radiopaque material. Significant pairwise differences between BA and BBM versus NC group are marked with asterisks (*P <0.05, **P <0.001).

Table 1 shows the result of radiographic analysis. Radiographic marginal bone/material level change at the 4-month primary end point was 0.36 ± 0.08 mm in the BA group as compared with -0.38 ± 0.16 mm in the NC group (significant difference P <0.05) and 0.14 ± 0.15 mm in the BBM group (no significant difference P >0.05). Figure 4 shows the radiographic marginal bone/material level change up to 12 months. In the BA group, radiographic marginal bone/material level was stable throughout the study period. In the BBM group, there was a slight increase in crestal bone/material level seen in the first 4 weeks but no significant change was observed after 4 weeks. In the NC group, a significant increase in crestal bone/material level was observed in the first 8 weeks but no significant change was observed after 8 weeks. A statistically significant difference was observed between the BA and NC group at all timepoints throughout the study. Between the BBM and NC group, a statistically significant difference

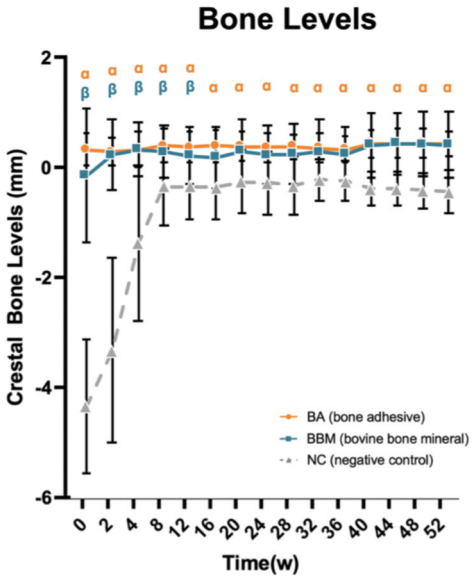

FIGURE 4 Mean crestal bone/material level change for one of three treatments from immediate post-op (0 weeks) to 52 weeks. Significant pairwise differences between BA and NC at each timepoint are marked with "α" and significant pairwise differences between BBM and NC at each timepoint are marked with "β"

was observed in only the first 12 weeks. Between the BA and BBM group, there was no statistically significant difference observed at any given timepoint. It is noted that there was 0.47 mm difference in the crestal implant position between the BA and BBM group at implant placement. However, that difference was not statistically significant.

Figure 5 shows an example of a 4-month periapical radiograph and the corresponding histological slide. This radiographic and histologic comparison, shows that the radiographic crestal bone/material level was correlated with the histologic crestal bone/material level. In this example, although the BBM site showed high radiopacity in the radiograph, an abundance of residual particulate graft was observed histologically and there was little to no new bone formation at the coronal one third of the implant. On the other hand, new bone formation in and throughout the BA and osseointegration of the implant was observed in all of the BA sites.

4 | DISCUSSION

Maintenance of crestal bone level is an important factor for the successful implant therapy and radiographic evaluation is widely accepted to assess any material placed around dental implant.[34] The objective of this study was to assess the crestal bone/material level of BA compared with BBM and to NC. The results of this radiographic analysis showed that BA and BBM demonstrated consistent crestal bone/material level from the time of implant placement up to 1 year whereas NC showed significant bone gain in first 8 weeks due to the resolution of bone defect caused by the oversized osteotomy. This bone gain stabilized after the 8-week timepoint and the NC sites presented with ≈ 0.4 mm crestal bone loss at 40 to 52 weeks. This finding is in agreement with a previous study done by Norton.[36] In a human immediate implant study without any bone grafting material, Norton reports a mean bone loss of 0.4 mm after a period of 15.7 to 27 months.[36] Thus, crestal bone loss occurred after immediate implant placement without

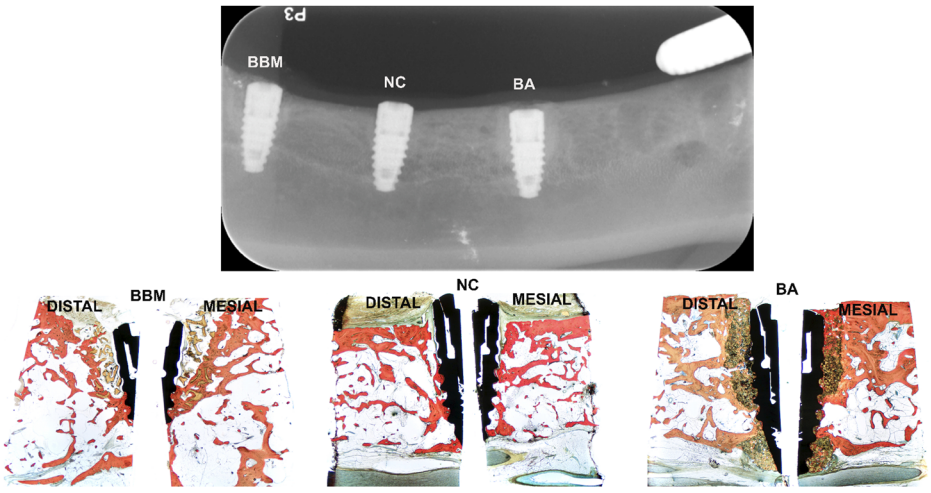

FIGURE 5 A standardized periapical radiograph at 4 months and corresponding low-power photomicrographs demonstrating the three experimental conditions (sagittal plane, ground section, Stevenel blue, and Van Gieson picro-fuchsin, original magnification 10×). In BBM, an abundance of residual particulate graft was observed and there was little to no new bone formation at the coronal one third of the implant. In NC, slight crestal bone loss was observed as shown in PA. In BA, new bone formation in and throughout BA and osseointegration of the implant was occurring

implantation of a biomaterial. However, direct comparison is not possible since none of the previous studies used the same canine model with oversized osteotomies for immediate implant placement without primary stability.

Previous in vitro studies showed that BA placed in a 90˚C water bath for 7 days (accelerated conditions) lost 20% its mass.[27] It can be speculated that a decrease in radiopacity may occur as BA around the implant is dissolved over a year if there was no bone formation to replace the biomaterial. The current study demonstrated continuous radiopacity around the implant stabilized with BA and suggests that BA is replaced by native bone as the biomaterial dissolves. This speculation was further validated with a histological analysis of the same cohort in the study by Cochran et al. and confirmed that new bone formation penetrated through BA and along the implant surface (osseointegration).[33] Although there was no statistically significant difference in terms of maintenance of crestal bone/material level between BA and BBM, BBM itself is an inert radiopaque material. Thus, while the radiographic bone/material level can be evaluated over time, it does not reveal the nature of the tissue surrounding the implant.[33]

Currently, there are no commercially available materials or devices that can provide instant stabilization for an implant placed in a fresh extraction socket that is lacking primary stability. In a previous publication using the same cohort group,[33] BA demonstrated a 20 Ncm reverse torque value at 24 hours from implant placement and 40 Ncm reverse torque value at 10 days post-implant placement both which were statistically significantly greater than BBM and NC. Arisan et al.[37] evaluated an injectable calcium phosphate cement (ICAP) to stabilize dental implants and found a 52-Ncm reverse torque value at 2 weeks. However, there was no statistically significant difference between the site with ICAP and without ICAP in terms of reverse torque values since the implant was placed with a conventional manner (no overseized osteotomy). Furthermore, the primary stability achieved at the time of implant placement made it difficult to evaluate the immediate stabilization obtained from ICAP. It should be noted that the BBM that was used in this study cannot be considered a "positive control" because neither this bone graft or any other material has been identified that can stabilize an implant placed into a large extraction site.

One of the challenges related to this study was to reproducibly create an implant that was lacking primary stability. To standardize placement of a mobile implant and to evaluate the effect of each condition, oversized osteotomies in a healed ridge were created in this study. However, the ultimate application of this material would be for stabilizing an immediate implant that is lacking stability in patients. The results of this study are not able to account for the ridge remodeling after a tooth is extracted. Therefore, further research is needed to determine if a continuous adhesion between BA and alveolar bone is maintained throughout the healing process following extraction.

5 | CONCLUSIONS

This study demonstrated that BA can provide a bone/biomaterial level equivalent to adjacent native bone immediately upon placement and that this level was maintained up to 1 year. This was in contrast to sites that contained BBM or NC where there was a healing period required where bone levels increased around the implant initially. Furthermore, highlighted analyses revealed that BA initiated contact with the implant surface and was replaced over time by bone (osseointegration) without a loss of crestal bone height. The findings from this radiographic study suggest that BA can create and maintain a hard tissue level, similar to adjacent native bone levels. These levels can be maintained for up to 1 year and may be replaced by bone.

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AUTHOR CONTRIBUTIONS

Ryushiro Sugita contributed to the design, execution of the procedures, data collection, and data analysis and wrote the article; Archie Jones contributed to the execution of the procedures and data collection; Georgios Kotsakis contributed to the data interpretation and review of the manuscript; David Cochran contributed to the concept, design, execution of the procedures, data interpretation, and review of the manuscript and provided supervision of the project.

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