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ORIGINAL ARTICLE

Histologic and histomorphometric evaluation of the bone regeneration following cortical bone repositioning in a rabbit mandible

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Abstract

Background: Although bone graft (BG) is the gold standard for bone augmentation, its use is hampered by donor site morbidity and limited quantity.

Purpose: To evaluate the capabilities of bone formation by cortical bone repositioning (CBR) as the healing response following grafting of autogenous bone block without filling biomaterial at the gap between gap and recipient.

Materials and Methods: Twelve Japanese White rabbits were divided into three groups (postoperative 2, 5, and 8 weeks). A cortical block was freed from the mandibular body, half of the block was positioned and fixed overlapped the original bone surface beside the defect and the other half remained only elevated above the defect. Three areas were decided for the evaluation; BG, CBR, and defect (D) area. Areas were evaluated by micro-CT, histology, and histomorphometric analysis.

Results: There is no statistical difference between BG and CBR by evaluating distance and area in histomorphometrical analysis ($P < .05$). D area showed statistical decrease compared with BG and CBR at week 2. Histologically, new bone was evident at week 2, mature bone was observed in all three areas at week 8, D area disappeared and fused completely with the elevated bone block.

Conclusion: CBR has potential for bone augmentation as BG induced from its own regenerative ability of healing process.

KEYWORDS
bone augmentation, bone grafting, bone regeneration, cortical bone repositioning

1 | INTRODUCTION

A variety of bone augmentation procedures have been described. Chiapasco et al described five methods for local bone volume augmentation at deficient sites[1]: osteoinduction using appropriate growth factors[2,3]; osteoconduction, in which a grafting material serves as a scaffold for new bone formation[4]; distraction osteogenesis (DO), in which a fracture is surgically induced and the two bone fragments are then slowly pulled apart,[5,6] guided bone regeneration, which allows spaces maintained by barrier membranes to be filled with bone[7,8]; and autogenous bone grafting, in which a vital bone segment is transferred to its recipient bed.[9,10]

Although autogenous bone grafting is the gold standard for bone augmentation, its use is hampered by donor side morbidity and the

limited quantity of harvestable bone.[10] Bone substitutes are available, but because of their material and chemical characteristics they cannot be used as widely as autogenous bone grafts (BGs).[11] The limited availability of soft tissue is problematic in cases of alveolar atrophy. When sufficient soft tissue to cover a graft is lacking, less surface area is available for revascularization, which is important to prevent resorption of grafted bone.[12] The ideal treatment protocol for bone augmentation is a single operation with no donor site morbidity that does not involve an artificial bone substitute to promote sufficient soft tissue formation.

Dynamic methods for bone augmentation, such as DO, have been developed to address the problems with bone grafting. DO, which was established by Ilizarov in the 1950s,[5,6] induces new bone formation following osteotomy and involves gradual lengthening of the bone segments. McCarthy et al introduced DO for the oral and maxillofacial area in 1992.[13] One of the most common characteristic findings of DO is the gap between the transport segment and original bone surface fills with newly formed bone without any biomaterials or autogenous bone substitute. This regenerative ability is based on bone healing process following bone fracture.

Applying the regenerative process at the gap between transport segment and original bone surface of DO, we investigate the technique of cortical bone repositioning (CBR) that induces bone regeneration at the static space created by lateral repositioning and rigid fixation of a cortical segment following corticotomy.[14] Unlike DO biology and its mechanism for osteogenesis, which are understood and consists of modulating the stress produced within the callus. The mechanism and biology of bone grafting and bone augmentation are not fully understood. The periosteum is equivalent to a physical barrier that effectively prevents other soft tissues from invading and is also conducive to the supplement of bone cells.[15] Bone augmentation can be achieved by the body's own healing mechanism and regenerative potency, the potential advantages of CBR are: no donor site required thus avoiding morbidity, full cover by soft tissue can be achieved, it does not need activation or management of a device and it can be done in a single procedure.

The aim of this study was to evaluate bone formation by CBR in comparison with conventional bone grafting, and to evaluate the osteogenic potential of the periosteum. The results will enhance our understanding of the biology of bone modeling and remodeling processes.

2 | MATERIALS AND METHODS

Twelve Japanese White rabbits (3-3.5 kg) were used. The study protocol and guidelines were reviewed and approved by the Animal Care and Use Committee of Tohoku University, Sendai, Japan in accordance with local laws and regulations, Approval number: 2017DnA-023.

Experiments were carried out in accordance with the guidelines established by the European Communities Council Directive of November 24, 1986 (86/609/EEC).

2.1 | Surgical protocol

The rabbits were anesthetized by intramuscular administration of ketamine hydrochloride (60 mg/kg Ketalar, Sankyo, Tokyo), followed by diazepam (5 mg) and atropine sulfate (0.5 mg), without endotracheal intubation. Before the operation, 10 mg/kg pentobarbital sodium was injected intravenously. In addition, 1.8 mL local anesthetic (2% xylocaine and epinephrine 1:80000, Dentsply Sankin, Tokyo, Japan) was used during all surgical procedures, which were performed under standard sterile conditions. The mandible was shaved and disinfected with 1% iodine sodium. After a submandibular approach to the body of the mandible, a rectangular cortical bone segment of 10 mm length and 4 mm width was designed and corticotomy was performed using a micro-saw.

The rectangular cortical bone block was elevated. Half of the block was positioned as a BG above the original bone surface beside the defect (D), and the other half was elevated only above the D area. The bone block was then fixed using two titanium screws (1.4 mm in diameter, 3 mm in length; Jeil Medical corp., Seoul, Korea), one on each side (Figure 1). The periosteum was returned to its original position and stabilized by careful suturing with 5-0 Vicryl (Johnson & Johnson,

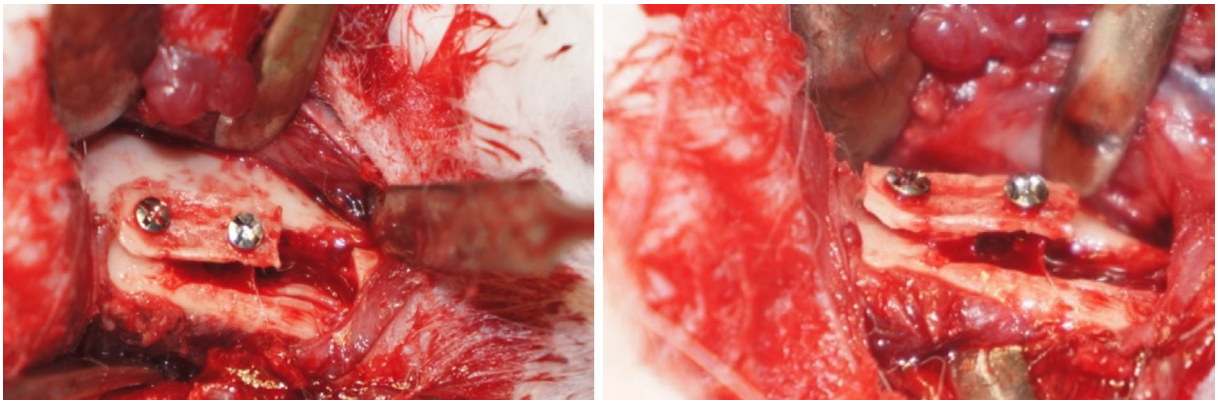

FIGURE 1 Schematic showing a lateral view of the surgical protocol. A cortical bone block was elevated from the surface of the mandible, transported laterally, and fixed with two mini titanium screws

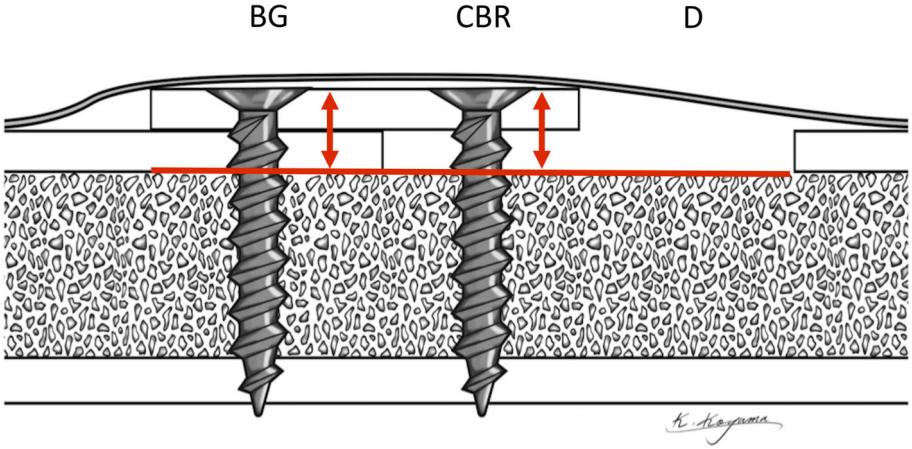

FIGURE 2 Schematic showing a lateral view of the surgical protocol. In the left side it's the BG area, in the center the CBR area, and in the right the D area, everything is covered by periosteum. The three evaluation areas are separated, red arrows represent the distance which was measured from the inner side of the cortex of the original bone surface to the outer side of the cortex of the elevated bone block. We used the same limits to measure the area. BG, bone graft; CBR, cortical bone repositioning; D, defect

Brussels, Belgium), the skin was closed using 4-0 Vicryl. All rabbits were given water and normal rabbit food postoperatively.

Rabbits were sacrificed at 2, 5, or 8 weeks postoperatively using a lethal dose of thiopental sodium.

Three areas of interest were examined: the BG, CBR, and D areas (Figure 2). The BG area corresponded to the area underneath the elevated bone block where the bone surface was located, the CBR area corresponded to the area underneath the elevated bone block where no bone surface was present, and the D area corresponded to the area with no bone surface or elevated bone block. The three areas were evaluated separately.

Bone formation was evaluated by micro-computed tomography (micro-CT) (Comscantechno, Co., Ltd., Yokohama, Japan) at 65 μA and 80 kV. Measurements of distance and area were made on three vertical images per specimen. Distance was measured from the inner side of the cortex of the bone surface to the outer side of the cortex of the elevated cortical bone block; area measurements also used these limits (Figure 2). New bone formation was measured in the three areas separately using image analysis software (ImageJ, ver. 1.47; NIH, Bethesda, MD).

2.2 | Tissue preparation

The rabbit mandibles were fixed for 14 days in 10% buffered formalin and decalcified in 10% ethylenediaminetetraacetic acid in phosphate-buffered saline at room temperature for 60 days. The specimens were dehydrated in ethanol, cleared in xylene, and subsequently embedded in paraffin. Sagittal sections of 5 μm thickness were cut with a microtome and mounted on glass slides. Hematoxylin and eosin (H&E) staining and tartrate-resistant acid phosphate (TRAP) staining were performed for morphological evaluation of newly formed bone in the gap between the original bone surface and the elevated cortical bone block.

2.3 | Statistical analysis

Normality and homogeneity were evaluated using variance analyses. An unpaired Student's *t*-test was used to analyze differences in distance and area values. The level of significance in all statistical tests was set at $P < .05$.

3 | RESULTS

No complications, including infection and active inflammation were observed during the course of the experimental period.

3.1 | Soft-focus CT evaluation

At 2 weeks (Figure 3A), new bone formation was detected by micro-CT as areas of lesser radiopacity than the original bone. In some specimens, new bone formation was present and no change was evident in the elevated bone block. At week 5 (Figure 3B), considerable new bone formation was evident, especially in the D area, and a bone bridge had formed between the elevated bone block and the opposite bone surface. All three areas remained well detailed and were easily defined. At week 8 (Figure 3C), a bone bridge connecting the elevated bone block with the original bone surface had also formed in the BG area. Furthermore, the height of the elevated bone block had decreased slightly, and more new bone had formed in the CBR and D areas. Surface height did not differ between the elevated bone block and the D area, unlike the week-5 findings.

3.2 | Histomorphometric analysis

Bone area increased in all three evaluation areas from weeks 2 to 5 and 8, except for the CBR area where a slight decrease was observed at week 8. By distance, we also observed that all evaluation areas increased from weeks 2 to 5 and 8, except for the BG area which had a slight decreased at week 8.

No statistical significance was observed between weeks 2, 5, and 8 in each of the evaluated areas. This indicates that no significant resorption of the elevated cortical bone block occurred between weeks 2, 5, and 8 at each of the evaluated areas. Statistical significance was observed between the evaluated areas, by distance there was a statistical significance between BG and D, CBR and D areas at

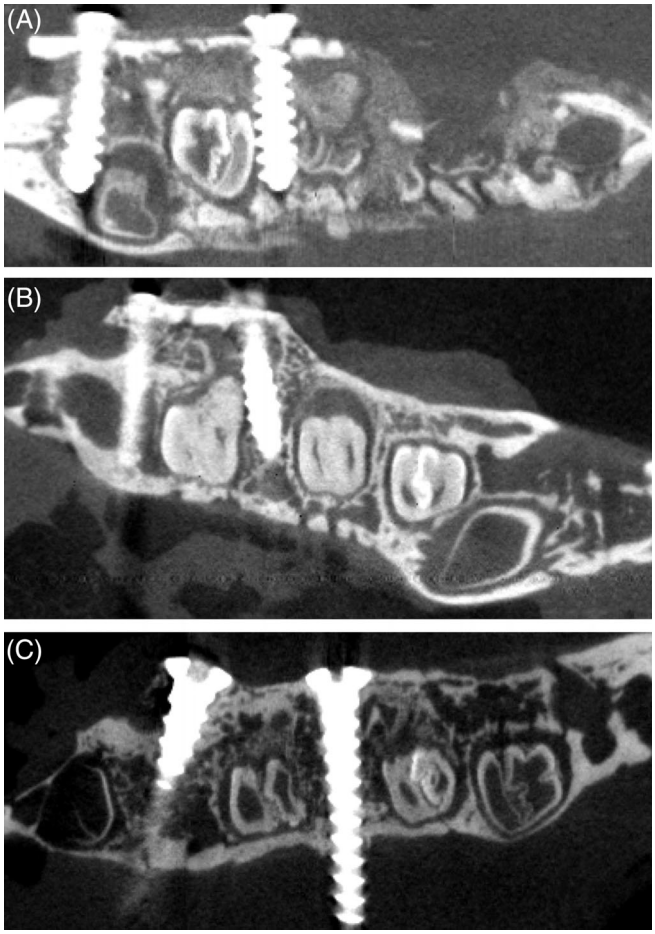

FIGURE 3 Soft focused X-ray CT images showing cross-sectional view. A, at week 2, the elevated bone block can clearly be observed at all evaluation areas. Some radiolucid areas can be seen nearby the D area and original bone surface. B, At week 5, great bone formation can be observed, the defect area disappeared completely and is now fused with the elevated bone block which remains intact, no resorption of the bone block can be observed. New bone can also be observed in the BG and CBR areas. C, At week 8, the surface level is the same in all three areas, it is difficult to identify each evaluated area as they mixed. Some resorption can be observed in the left edge of the BG area. It is important to notice that the mini titanium screw head is still in direct contact with the bone surface, this means that the elevated bone block suffered little resorption. BG, bone graft; CBR, cortical bone repositioning; D, defect

weeks 2, 5, and 8. By area there was a statistical significance between BG and D, CBR and D areas at week 2 (Figures 4 and 5).

3.3 | Histological evaluation

Histological findings of each area are shown in Figure 6. New bone formation was evident beginning at week 2, and multiple scattered bony trabeculae were present in all three areas and above the elevated bone block, the D area was filled with fibrous tissue, with bony trabeculae beneath. At week 5, woven and trabecular bone were observed, particularly in the D area. At week 8, mature bone was observed in all three areas, the D area disappeared and fused

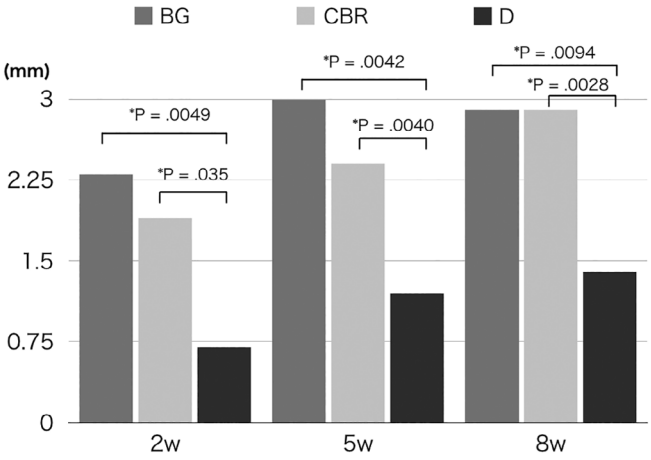

FIGURE 4 Results by distance (mm) of BG, CBR, and D areas at 2, 5, and 8 weeks. BG, bone graft; CBR, cortical bone repositioning; D, defect

completely with the elevated bone block. No inflammatory cell reaction was observed in any of the three areas. TRAP staining revealed osteoclast activity during bone remodeling in all three areas at weeks 2 and 5. At week 8, osteoclast activity was barely observed or completely absent in all three areas of interest (Figure 7).

4 | DISCUSSION

Bone augmentation procedures can be divided into static and dynamic methods. The gold standard method used today is still the autogenous BG, as it is inexpensive, predictable, and convenient, and has a good prognosis.[10] The complications of bone grafting include bone resorption, donor site morbidity, and problems with soft tissue. Patients with severe atrophic ridge have some risks for bone resorption and difficulty with soft tissue coverage that have a risk of following wound dehiscence. In such cases, a dynamic method such as DO is applied

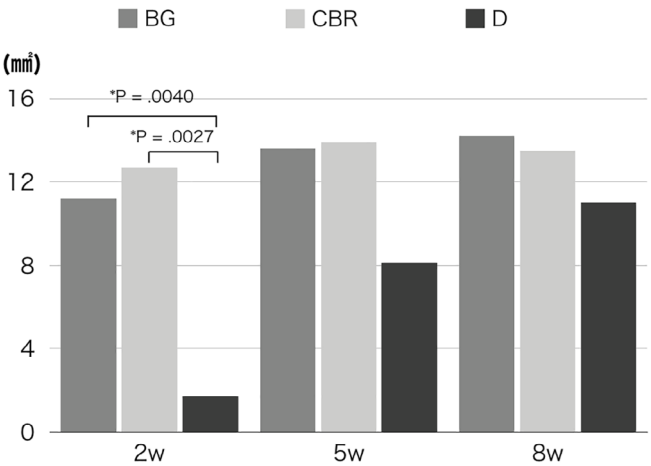

FIGURE 5 Results by area (mm^2) of BG, CBR, and D areas at 2, 5, and 8 weeks. BG, bone graft; CBR, cortical bone repositioning; D, defect

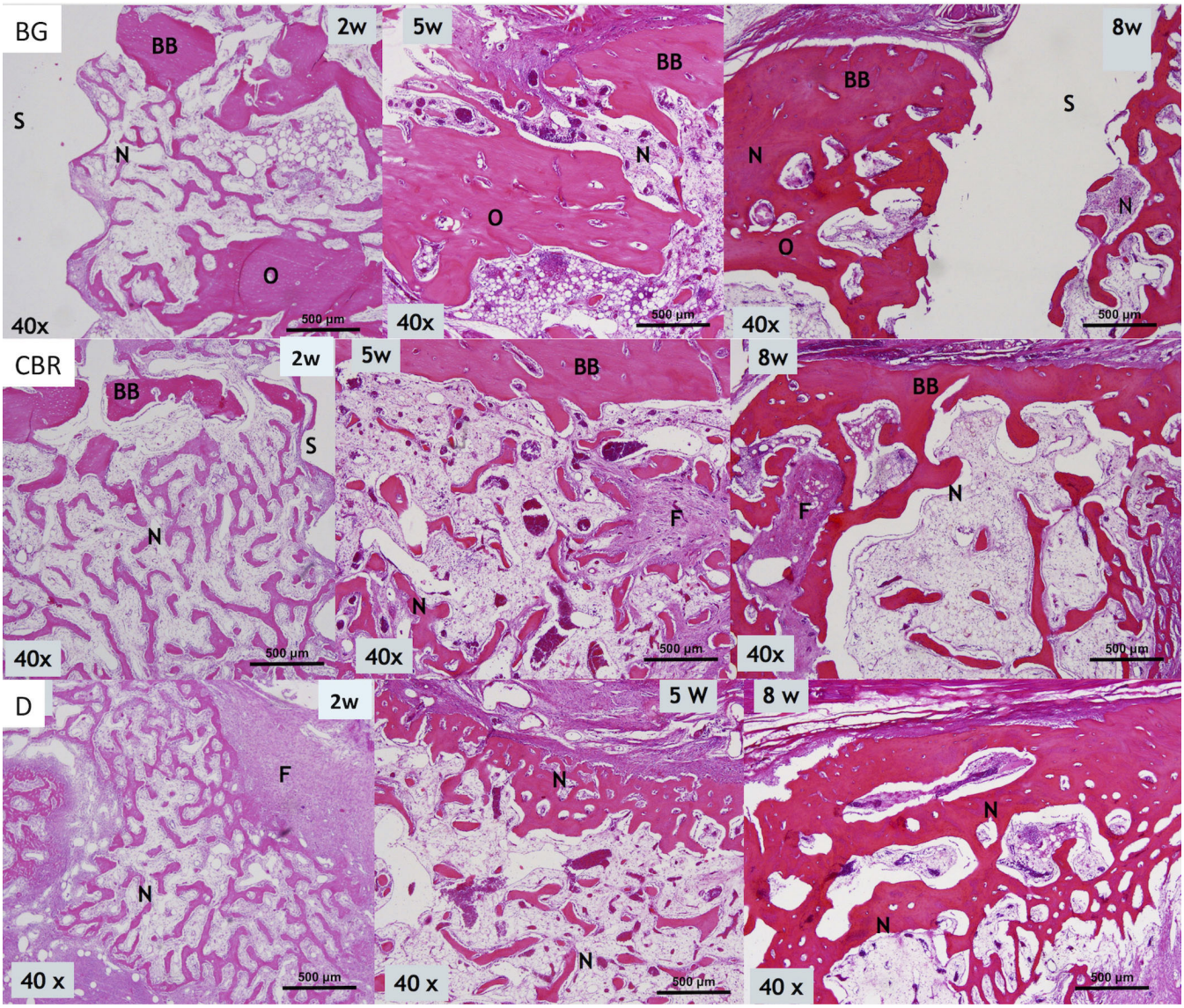

FIGURE 6 Hematoxylin and eosin staining of the BG, CBR, and D areas at 2, 4, and 8-week comparison. S: screw, O: original bone, N: new bone, BB: bone block D: defect, F: fibrous tissue. Magnification; 40×, 500 µm. BG, bone graft; CBR, cortical bone repositioning; D, defect

because of the advantage of simultaneous lengthening of the surrounding soft tissue.[16,17] However the clinical criteria to choose between a static or dynamic method is not clear, Lethaus et al found no significant difference in bone formation between both methods.[18]

CBR implements aspects of these two methods in a single stage involving static movement and fixation of a bone segment (ie, a BG), without using a donor site. CBR involves a one-stage traction. Stable fixation of the bone segment is important for the success of CBR. Another static bone augmentation method is the split crest technique, Nentwig et al reported a bone-crest division technique that allows simultaneous expansion of the alveolar crest and implant insertion,[19] however, soft tissue cannot fully cover the expanded ridge, thus affecting the periosteal blood supply and therefore the blood supply of the bone cortex. Adequate blood supply plays a critical factor in bone regeneration and fracture healing, Marenzana et al reported that inadequate blood supply to the bone resulted in local hypoxia which may be maintained by subsequent inflammation.[20] In our experimental study with CBR and periosteal elevation, both of these problems are not present, the alveolar process was covered completely by a thick layer of soft tissue and no inflammation was observed.

The bone lid technique has been used in a variety of procedures in oral surgery and it is known to improve the bone healing process by offering a secluded space where osteogenic cells can easily repopulate the wound, preventing connective tissue ingrowth, and thus working as an autogenous barrier membrane.[21,22] CBR technique also uses a cortical segment repositioning not to the original but intentional lateral position. CBR involves creation of a space-maker under the periosteum by transporting and fixing in place a segment of the cortex. The osteogenic potential of the periosteum plays a key role in osteogenesis, and the periosteum is an important source of osteoblasts and osteoblast precursor cells.[23] Elevation of the periosteum from the underlying bone produces tension on the periosteum, which triggers

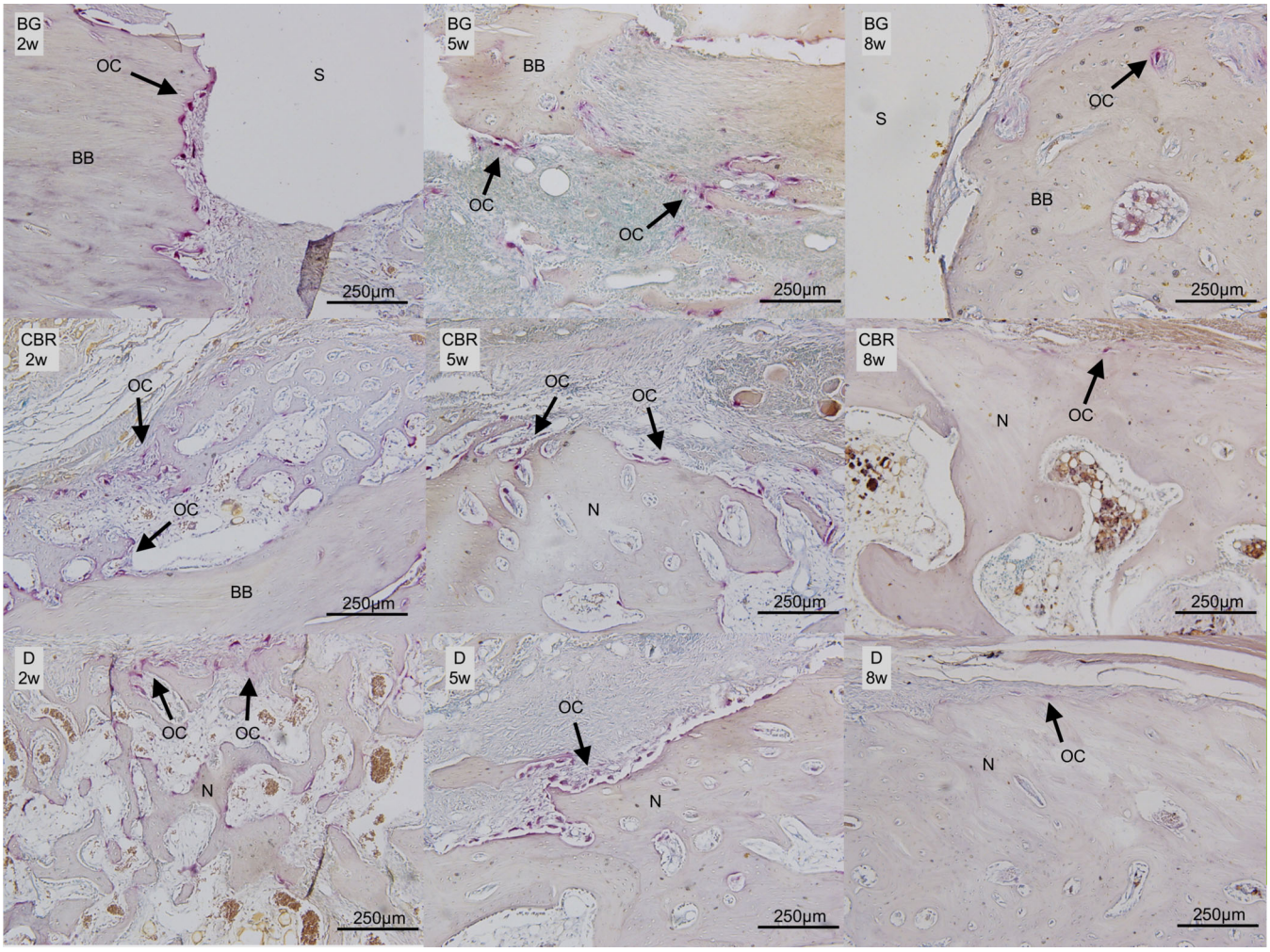

FIGURE 7 Tartrate-resistant acid phosphatase staining. Osteoclast activity due to bone remodeling comparison, 2, 5, and 8 week in each evaluated area. Weeks 2 and 5 osteoclast activity can be observed in every evaluated area. At week 8 all areas show barely any osteoclast activity. OC: osteoclast, N: new bone, BB: bone block. 100×, 250 µm

mesenchymal stem cells to differentiate into osteoblasts, resulting in subperiosteal bone formation. Mechanical elevation of the periosteum without corticotomy is therefore sufficient to generate new bone.[24-27] CBR tensions and elevates the periosteum to create a space beneath. Furthermore, movement of a bone segment induces an inflammatory reaction that triggers bone remodeling by osteoclasts and osteoblasts.

In this study, the D area, which lacked a bony surface and was covered only by an elevated layer of periosteum under tension, exhibited the most new bone formation from week 2 to 8. This result demonstrates the osteogenic potential of the periosteum, the body's regenerative bone healing ability. The D area had disappeared at week 5, and a bridge of newly formed bone that connected the elevated bone block with the opposite bone surface had formed. The different surface heights of the two segments resulted in increased bone formation in the CBR and D areas; all three areas had identical surface elevations at week 8 in most specimens. Maintenance of a space under the periosteum by the elevated bone block in CBR is similar to the tent-pole technique.

The height of the elevated bone block did not decrease, as the head of the mini-screw remained in contact with the elevated bone block at week 8 (Figure 5C). Despite this contact, some resorption was evident at week 8, mainly at the edges of the bone block in the BG and CBR areas. Both edges were remodeled into smooth, round forms. Takeuchi et al demonstrated that more newly formed bone was achieved when the periosteum was preserved than when it was removed, and that the preservation of the periosteum also prevented bone resorption.[28] Moreover, bone remodeling activity was active at weeks 2 and 5 in all evaluated areas, but had decreased considerably at week 8, as seen in the TRAP images.

Autogenous BGs are frequently (in 25-60% of cases) resorbed at the recipient site.[29] Resorption depends on multiple factors such as origin and type of graft, placement location and muscle activity; for instance, it has been reported that the resorption of iliac crest BGs for onlay augmentation is significantly more pronounced in the maxilla than in the mandible.[30,31] It has also been observed that resorption of block BGs from the chin and ramus did not differ, while chin grafts showed a significantly more pronounced resorption compared to iliac

crest BGs.[32] Calvarial BGs have been associated with minimal resorption, however, Carinci et al found that after 30 months, the difference in resorption was no longer statistically significant compared with iliac crest BGs.[33] Inlay bone grafting has a significantly lower loss in vertical dimension than onlay bone grafting.[34] Resorption is an inherent consequence of graft healing and incorporation into the osseous recipient site. Such sites demonstrate a specific bone remodeling pattern that closely resembles fracture healing.[35] The mechanism underlying block graft resorption is unclear, but factors such as the graft microarchitecture may influence the degree of vascularization during healing.[36] The resorption observed at the edges of the elevated bone block in the CBR and BG areas could be due to the curved surface of the rabbit mandible and muscle activity. Such curvature can result in variations in the position, angle, elevation, and/or distance of the elevated bone block, which in turn complicates evaluation of the results.

The acceptable distance between the elevated bone block and the original bone surface for the induction of new bone formation is unclear. We are attempting to identify the limits of CBR; for example, at what elevation will the bone block convert into a sequestrum, thereby preventing new bone formation? When is a static method for periosteal DO indicated instead of a dynamic method? Further studies are needed to determine the indications for static and dynamic DO methods for periosteal bone augmentation. Such studies should take into consideration several factors, such as the vascularity, location, size, and width of the bone block.

5 | CONCLUSION

CBR makes use of the body's regenerative ability to induce bone healing. The advantages of CBR include the need to perform only a single procedure, the use of a minimal amount of materials (only fixation screws), the lack of donor site morbidity, and the lack of a need for postoperative activation. In this study, CBR showed considerable promise and the findings enhance our understanding of the bone remodeling process. However, few studies have assessed CBR; therefore, further research is necessary.

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The authors explicitly declare that there is no conflict of interest in connection with this article.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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