Research Article

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The biological effect of cyanoacrylate-combined calcium phosphate in rabbit calvarial defects

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Purpose: The purpose of this study was to determine the biological effects of cyanoacrylate-combined calcium phosphate (CCP), in particular its potential to act as a physical barrier - functioning like a membrane - in rabbit calvarial defects.
Methods: In each animal, four circular calvarial defects with a diameter of 8 mm were prepared and then filled with either nothing (control group) or one of three different experimental materials. In the experimental conditions, they were filled with CCP alone (CCP group), filled with biphasic calcium phosphate (BCP) and then covered with an absorbable collagen sponge (ACS; BCP/ACS group), or filled with BCP and then covered by CCP (BCP/CCP group).
Results: After 4 and 8 weeks of healing, new bone formation appeared to be lower in the CCP group than in the control group, but the difference was not statistically significant. In both the CCP and BCP/CCP groups, inflammatory cells could be seen after 4 and 8 weeks of healing.
Conclusions: Within the limits of this study, CCP exhibited limited osteoconductivity in rabbit calvarial defects and was histologically associated with the presence of inflammatory cells. However, CCP demonstrated its ability to stabilize graft particles and its potential as an effective defect filler in bone augmentation, if the biocompatibility and osteoconductivity of CCP were improved.

Keywords: Octylcyanoacrylate, Calcium phosphate, Rabbits, Bone regeneration.

INTRODUCTION

Bone-grafting techniques have become essential in the restoration of both function and esthetics in the treatment of maxillofacial osseous defects. In dentistry, it has been used widely to treat periodontal osseous defects and to regenerate the bone necessary to permit placement of implants, such as sinus grafts and guided bone regeneration [1-3]. Although autogenous bone has excellent osteogenic properties and elicits no immune response, it has several disadvantages and limitations with regard to patient morbidity, harvest quantity, and complications such as paresthesia and infection. Researchers have been working to develop the ideal substitute for autogenous bone. Synthetic materials have been suggested as alternatives and have been investigated for with adequate osteoconductive properties.

Cyanoacrylates have been used successfully as tissue adhesives in various surgical applications [4,5]. It has also been reported that cyanoacrylate has hemostatic and antibacterial properties [6,7] when used instead of traditional suture materials to close surgical wounds. Many recent investigations have found that cyanoacrylate does not induce tissue toxicity when it is used as a wound dressing for the treatment of open wounds as well as wound closure [8-10]. Kutcher [11] re-

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ported that devices utilizing cyanoacrylate were safe and effective for pain relief in oral ulcerations. According to Bhaskar et al. [12], the application of cyanoacrylate spray to the oral mucosa did not induce any adverse effects in the surrounding tissues.

It has recently been suggested that synthetic materials produced using cyanoacrylate can be used as a bone substitute for the restoration of osseous defects. Lee et al. [13] reported that rat calvarial defects reconstructed with cyanoacrylate-combined calcium phosphate (CCP) demonstrated new bone formation, and Park et al. [14] revealed that CCP could be a candidate for osseous healing in bone defects. CCP is prepared by mixing liquid cyanoacrylate and inorganic bioceramic powders. This material has unique properties different from those of conventional bone substitutes. Traditional granular-type bone substitutes may be lost and are difficult to manipulate when applied to osseous defects that are especially large or that have a limited bony wall for supporting the graft materials. Conversely, because of its plasticity, adhesiveness, and rapid hardening properties (hardens within 3 to 5 minutes), CCP can prevent such loss of graft particles and is easily manipulated within osseous defects. In addition, when it is used in combination with different kinds of alloplasts or allografts, CCP is able to bind to and immobilize other graft materials within the defect. It is thus possible to consider CCP a physical binder that can prevent loss of graft particles, like a plastic membrane. CCP is also more advantageous than a block-type bone substitute, which is difficult to plasticize in nonstandardized osseous defects. CCP has physical and mechanical benefits; however, clinical and histologic evaluations of this material as a bone-graft material are lacking. Furthermore, although cyanoacrylate has been used effectively and reliably for the closure of superficial wounds and lacerations, the biocompatibility of cyanoacrylate as an implant material in vivo has not yet been established.

The purpose of this study is to histologically determine the biologic effects of a novel CCP material and its potential as a physical binder in surgically prepared rabbit calvarial defects.

MATERIALS AND METHODS

Animals

Twelve adult male New Zealand white rabbits weighing 2.5 to 3.0 kg were used. All animals were given a 1-week period of adaptation before the start of the surgical procedure. The animal selection and management, surgical protocols, and preparation followed the protocols approved by the Institutional Animal Care and Use Committee, Yonsei Medical Center, Seoul, Korea (08-167).

Graft materials

CCP was prepared by mixing two pastes: one containing 0.1 g of liquid cyanoacrylate and solid inorganic materials, the other containing 0.22 g of osteoconductive β-tricalcium phosphate (β-TCP) with a particle size of 10 to 50 μm and 0.14 g of glycerin. Inorganic materials in the first paste comprised 0.23 g of monocalcium phosphate (particle size 50 to 100 μm) and 0.03 g of dicalcium phosphate (particle size 10 to 20 μm).

Biphasic calcium phosphate (BCP; Osteon, Genoss Co., Suwon, Korea) with a hydroxyapatite (HA)/β-TCP ratio of 70/30, a porosity of 77%, and a pore size of 300 to 500 μm was used in this study. The HA in this BCP was coated with β-TCP. An absorbable collagen sponge (ACS; Collatape, Zimmer Dental, Carlsbad, CA, USA) was used to cover the bone substitute.

Study design

Four circular defects, each with a diameter of 8 mm, were prepared in each rabbit calvarium (Fig. 1). Each of the four defects in each animal was immediately filled with different graft materials according to the experimental condition, as follows (the location of the implant material in each animal was assigned randomly). The animals underwent a healing period of either 4 or 8 weeks (six animals per group for each period).

1. Control group (12 defects): defects were left unfilled, to serve as the surgical control.
2. CCP group (12 defects): defects were filled with only CCP.
3. BCP/ACS group (12 defects): defects were filled with BCP and then covered by ACS.
4. BCP/CCP group (12 defects): defects were filled with BCP and then covered by CCP.

Surgical procedures

All animals were anesthetized using an intramuscular injection of a mixture of ketamine hydrochloride (Ketar, Yuhan,

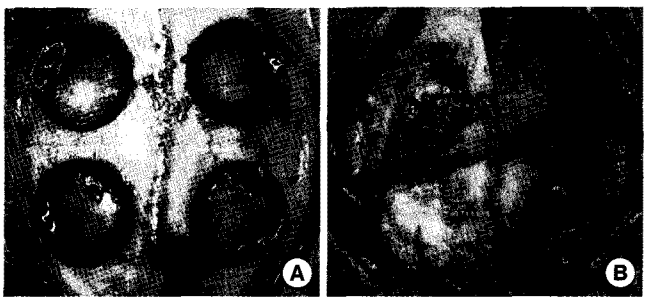

Figure 1. Clinical photographs of defect preparation (A) and application of the experimental materials (B). CCP: cyanoacrylate-combined calcium phosphate, BCP: biphasic calcium phosphate, ACS: absorbable collagen sponge.

Seoul, Korea) and xylazine (Rumpun, Bayer Korea, Seoul, Korea). The head of the rabbit was shaved and disinfected with povidone iodine. An incision was made along the midline of the parietal bone from the frontal bone to the occipital bone. A full-thickness flap was elevated. Under copious saline irrigation, four standardized round defects, each 8 mm in diameter, were created using a trephine bur (Fig. 1). The resected bones were removed carefully to avoid injury to the underlying brain tissue. The interdefect distance was more than 4 mm, allowing normal healing and easy harvest of the specimens for histologic analysis. The defects were filled with different experimental materials, depending on the study group (see above). The flaps were repositioned and sutured with resorbable suture material (Polyglactin 910, braided absorbable suture, Ethicon, Johnson & Johnson, Edinburgh, UK). The animals were sacrificed at either 4 or 8 weeks postsurgery. The skin flaps were then reflected and the entire calvarium was harvested from each animal using a small sharp fissure bur.

Histological processing

Block sections of the surgical sites were fixed in 10% formalin for 10 days. The fixed specimens were decalcified in 5% formic acid for 14 days and then embedded in paraffin. Serial, 5-μm-thick sections were cut along the midline of the calvarial defects. Only sections located at the middle of the defect were selected, and these were stained with hematoxylin-eosin for histologic and histometric analysis.

Analysis

Clinical observations; Visual observations were performed after 4 and 8 weeks of healing for clinical evaluation.

Radiologic analysis; After sacrificing the animals, all specimens were radiographed using an X-ray machine for descriptive radiographic analysis.

Histologic analysis; Histologic slides were examined with the aid of a binocular microscope (Leica DM LB, Leica Microsystems, Wetzlat, Germany) equipped with a camera (Leica DC300F, Leica Microsystems, Heerbrugg, Switzerland). The slides were photographed and the obtained images saved as JPEG files.

Histometric analysis; Histometric measurement was performed using an automated image-analysis computer program (Image-Pro Plus, Media Cybernetics, Sliver Spring, MD, USA). The augmented area (all tissue within boundaries of the defect: newly formed bone, residual graft material, connective tissue, bone marrow) and new bone area (mm^2; Fig. 2) were measured.

Statistics

The mean and standard deviation of values for each group were calculated. The significance of differences between groups was determined using the Kruskal-Wallis test ($P<0.05$). The Mann-Whitney test was used to analyze the differences between values at 4 and 8 weeks. The Bonferroni correction was used to analyze differences that were significant at the 5% level ($P<0.05$).

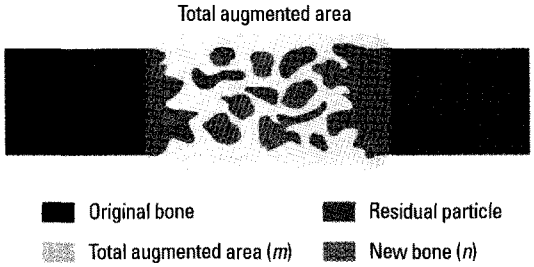

Figure 2. Schematic diagram of a calvarial osteotomy defect showing the histometric analysis. New bone area (mm^2)=n; residual biomaterial, fibrovascular tissue, bone marrow=m; augmented area (mm^2)=$n+m$.

RESULTS

Clinical observations

Healing was uneventful for all animals during the postoperative period. None of the animals exhibited any complications such as infection or exposure of the graft material after surgery.

Radiologic observations

In the control group, a small radiopaque area was observed from the defect border after 4 weeks of healing; this area had increased after 8 weeks of healing. In the CCP group, a large radiopaque area surrounded by a radiolucent rim was observed after 4 weeks of healing. There was an overall decrease in the radiopaque area at 8 weeks. In the BCP/ACS group, radiopaque graft particles were densely packed and there was no significant difference between the findings after 4 and 8 weeks of healing. In addition, the radiographic appearance of the BCP/CCP-filled defects was very similar to that of the BCP/ACS-filled defects, except that the former was slightly more radiopaque (Fig. 3).

Histologic analysis

Control group; A slight bony ingrowth from the border of the defects that appeared to proceed to the central portion was observed in the control group. Most of the area of the defects was filled with fibrous connective tissue that interconnected with both defect margins. The space observed within the defect did not persist, collapsing during the healing period. Some specimens exhibited bony islands within

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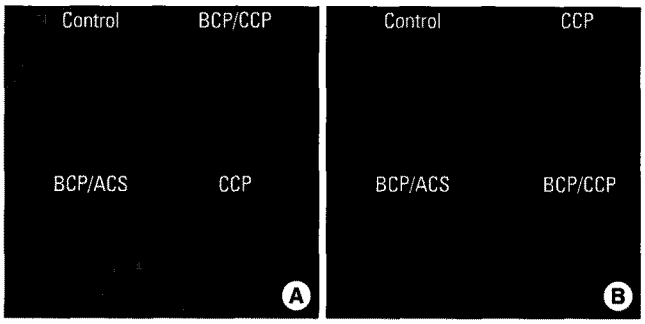

Figure 3. Radiologic presentation of calvarial defects after 4 weeks (A) and 8 weeks (B) of healing. CCP: cyanoacrylate-combined calcium phosphate, BCP: biphasic calcium phosphate, ACS: absorbable collagen sponge.

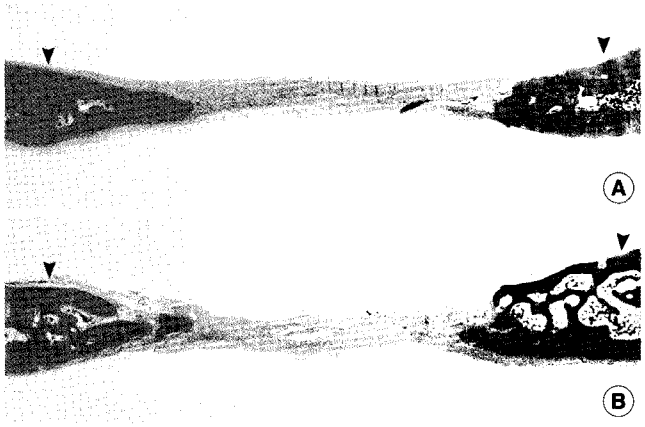

Figure 4. Histologic presentation of a specimen from the control group after 4 weeks (A) and 8 weeks (B) of healing. Slight bony ingrowth can be seen from the border of the defects, along with collapse of the connective tissue (A, H&E, ×10; B, H&E, ×10). arrowheads, defect margin.

the defects. The amount of new bone observed was greater after 8 weeks than after 4 weeks of healing (Fig. 4).

CCP group; There was a minimal amount of newly formed bone in the CCP group, and an inflammatory response was detected within the defects. When viewed at a higher magnification, inflammatory cells such as multinucleated giant cells, neutrophils, and lymphocytes were detected. The inflammatory reaction persisted at the 8-week follow-up (Figs. 5, 6).

BCP/ACS group; A bony ingrowth originating from the periphery of the defect was observed in the BCP/ACS group, with immature woven bone in close contact with the graft particles. The regenerated bone contained many osteocytes, and osteoblastic cells surrounded the graft materials. The amount of new bone formation was greater after 8 weeks than after 4 weeks of healing (Figs. 7, 8).

BCP/CCP group; Histologic findings of the BCP/CCP group were very similar to those of the CCP group. Many inflammatory cells were seen, and there was limited bone formation, which was seen only at the defect margin. Moreover, immature woven bone was only barely observed around the BCP particles, in contrast to the BCP/ACS group (see above). Comparison of the specimens after 4 and 8 weeks of healing revealed them to be histologically indistinguishable from each other (Figs. 9, 10).

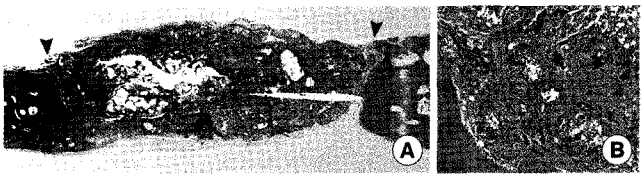

Figure 5. Histologic presentation of the cyanoacrylate-combined calcium phosphate group after 4 weeks of healing. A limited amount of new bone formation and inflammatory infiltration can be seen (A, H&E, ×10; B, H&E, ×100). arrowheads, defect margin.

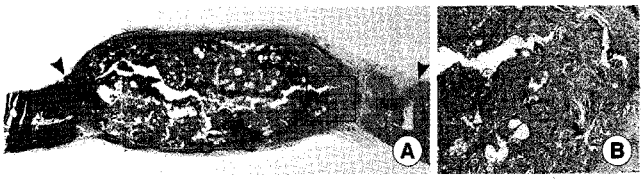

Figure 6. Histologic presentation of the cyanoacrylate-combined calcium phosphate group after 8 weeks of healing (A, H&E, ×10; B, H&E, ×100). arrowheads, defect margin; NB: new bone.

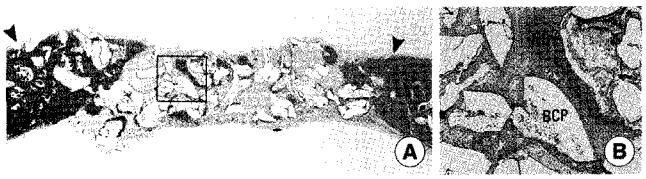

Figure 7. Histologic presentation of the biphasic calcium phosphate (BCP)/absorbable collagen sponge group after 4 weeks of healing. New bone is seen in close contact with the graft material (A, H&E, ×10; B, H&E, ×100). arrowheads, defect margin; NB: new bone, BCP: biphasic calcium phosphate.

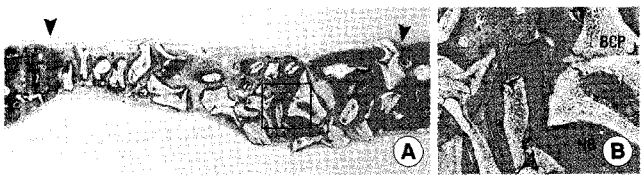

Figure 8. Histologic presentation of the biphasic calcium phosphate (BCP)/absorbable collagen sponge group after 8 weeks of healing. Enhanced and mature bone surrounds the graft materials (A, H&E, ×10; B, H&E, ×100). arrowheads, defect margin; NB: new bone, BCP: biphasic calcium phosphate.

Histometric analysis

The results of the histometric analysis are presented in Table 1. The augmented area in the control group was smaller

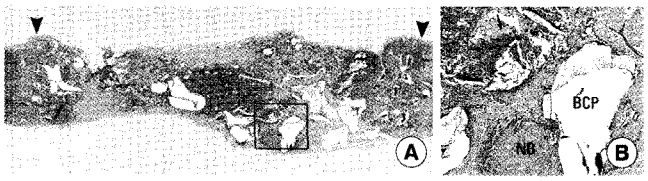

Figure 9. Histologic presentation of the biphasic calcium phosphate (BCP)/cyanoacrylate-combined calcium phosphate group after 4 weeks of healing. Limited bone formation is observed at the defect margin and in contact with the BCP materials (A, H&E, ×10; B, H&E, ×100). arrowheads, defect margin; NB: new bone.

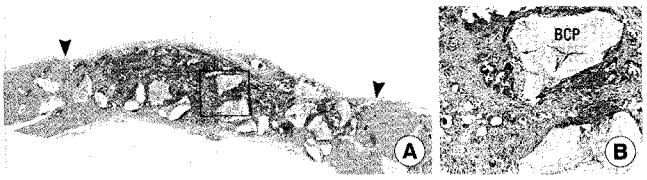

Figure 10. Histologic presentation of the biphasic calcium phosphate (BCP)/cyanoacrylate-combined calcium phosphate group after 8 weeks of healing. The connective tissue is infiltrated with inflammatory cells (A, H&E, ×10; B, H&E, ×100). arrowheads, defect margin.

to that of the experimental groups, with a new bone area of 1.04±0.69 mm² after 4 weeks and 2.29±0.86 mm² after 8 weeks of healing. Although the amount of bone increased with healing time (i.e., 4 and 8 weeks), the difference was not statistically significant. The mean bone regeneration in the CCP group was lower than in the control group after both 4 and 8 weeks of healing. After 8 weeks of healing in the CCP group, an increase was observed in the area of new bone, but again this change was minimal and not statistically significant. Meanwhile, a significant increase in the area of new bone was observed in the BCP/ACS group, from 2.10±0.38 mm² after 4 weeks of healing to 2.84±1.24 mm² after 8 weeks. The amount of new bone found in the BCP/CCP group was 1.26±0.93 mm² and 0.64±0.31 mm² after 4 weeks and 8 weeks of healing, respectively. A statistically significant difference in new bone formation was found between the BCP/CCP and BCP/ACS groups after 8 weeks of healing. The mean bone regeneration in the CCP group was significantly lower than in the BCP/ACS group after both 4 and 8 weeks of healing.

DISCUSSION

This study evaluated the biological effects of CCP in the treatment of rabbit calvarial defects. Various homologues of cyanoacrylate compounds exist, such as methylcyanoacrylate, ethylcyanoacrylate, butylcyanoacrylate, and octylcyanoacrylate. Cyanoacrylate with a longer carbon side chain has a slower degradation rate and also a lower toxicity [15]. Only

Table 1. Histometric results after 4 and 8 weeks of healing.

Parameter	Control	CCP	BCP/ACS	BCP/CCP
4 wk (n=6)				
Augmented area	5.07±1.25	15.30±5.13[a)]	11.11±0.96	19.09±3.85[a),b)]
New bone area	1.04±0.69	0.4±0.17[b)]	2.10±0.38	1.26±0.93
8 wk (n=6)				
Augmented area	5.52±1.87	12.24±1.88[a)]	10.50±1.81[a)]	14.43±1.89[a),c)]
New bone area	2.29±0.86	0.75±0.58[b)]	2.84±1.24	0.64±0.31[b)]

Values are presented as mean±SD.
CCP: cyanoacrylate-combined calcium phosphate, BCP: biphasic calcium phosphate, ACS: absorbable collagen sponge.
[a)] Significant statistical difference compared to control group at each week ($P<0.05$).
[b)] Significant statistical difference compared to BCP/ACS at each week ($P<0.05$).
[c)] Significant statistical difference compared to 4 weeks ($P<0.05$).

butylcyanoacrylate and octylcyanoacrylate have been used thus far in medical and dental applications. In particular, 2-octylcyanoacrylate was approved by the Food and Drug Administration in 1998 and was reported to be a well-established tissue adhesive for surgical wound closure [8]. The CCP used in this study also contained liquid 2-octylcyanoacrylate and was manufactured by combining 2-octylcyanoacrylate with several inorganic calcium phosphates. The monocalcium phosphate in this particular CCP controls the velocity of polymerization. This was necessary, since cyanoacrylate rapidly polymerizes and hardens when it is exposed to moisture at room temperature. The addition of monocalcium phosphate extends the working time necessary to manipulate the CCP in order to fill defects. The polymerization and hardening of CCP takes approximately 3 minutes. Among the several other calcium phosphates in CCP, dicalcium phosphate serves as a filler, and β-TCP, which is a well-established osteoconductive synthetic biomaterial that has been demonstrated to be absorbed *in vivo* and replaced with new bone, [16,17] is also added to CCP.

The defects reconstructed by only CCP exhibited a limited amount of new bone formation compared to the control group after both 4 and 8 weeks of healing. A slight increase was observed at 8 weeks but was not statistically significant. Inflammatory infiltrates with numerous multinucleated giant cells, lymphocytes, and neutrophils were observed in the histologic specimens. Although healing progressed to 8 weeks, the extent of inflammation was constant.

A recent study that investigated the same material in a canine model found similar results to the present study, wherein CCP resulted in slight bone and cementum regeneration in periodontal one-wall intrabony defects [18]. Lee et al. [13] reported no inflammatory response in a defect filled with a cyanoacrylate-based filling material, and further, new bone formation was observed in rat calvarial defects. These incon-

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sistent findings are presumably due to differences in the experimental materials, namely N-butyl-2-cyanoacrylate and β-TCP used in the study of Lee et al. [13]. According to those authors, when this compound was mixed, the temperature generated during the polymerization did not increase significantly relative to that generated during the polymerization of N-butyl-2-cyanoacrylate alone. It has been reported that the polymerization process of cyanoacrylate generates heat that could damage the cells and surrounding tissues, ultimately accounting, at least in part, for the cytotoxicity of cyanoacrylate [15]. The exothermic properties of CCP *in vivo* have not yet been verified. However, it is possible that the heat released during the polymerization of CCP is associated with the inflammatory response observed in our histologic analysis. Another possible explanation for this finding is a foreign-body reaction to the 2-octylcyanoacrylate itself, when it is implanted *in vivo*. Dragu et al. [19] reported a foreign-body reaction when a tissue adhesive composed of 2-octylcyanoacrylate was applied to a wrist laceration wound, and identified inflammatory histopathologic results.

On the other hand, it has been reported that cyanoacrylate has hemostatic properties and could be considered a therapeutic option for the prevention of microvascular bleeding and postoperative hemorrhage in surgical procedures [20-22]. However, this means that the hemostatic effect of cyanoacrylate may ironically reduce the osteoconductivity of CCP. New bone formation is achieved by providing the synthetic material with a sufficient blood supply, and so this hemostatic effect may in some way be responsible for the minimal new bone formation found in the CCP group. However, further investigation is necessary to verify whether the hemostatic effects of cyanoacrylate can adversely influence the osteoconductivity of CCP.

The defects reconstructed with BCP and ACS exhibited statistically significant new bone formation after both 4 and 8 weeks of healing, compared to the CCP group. There was also statistically significant bone formation at 8 weeks when compared to the BCP/CCP group. Histologically, grafts exhibited many osteoblasts surrounding the graft material, and immature woven bone. The maturity and quantity of new bone increased with healing time. These histologic and histometric results concur with those of previous studies demonstrating the osteoconductive effects of BCP in both clinical and animal experiments [23-25].

The ACS that was applied to cover the BCP was completely biodegraded within 10 to 14 days. During this period it was possible to separate the bone graft material from the cutaneous flap and prevent graft particles from escaping the defects. In our previous study, we confirmed that placement of the ACS over the particles was an effective method for accelerating bone regeneration in canine one-wall periodontal intrabony defects [26]. Moreira-Gonzalez et al. [27] described the importance of maintaining graft particles, finding that the migration of particles into the surrounding tissue resulted in limited bone regeneration. The ability of CCP to act as a mechanical binder and physical barrier to keep the graft materials within the defect was also evaluated by comparing it to ACS with regard to bone regeneration. Histologic observations of the BCP/CCP groups showed that the BCP granules located under CCP were stably maintained without migrating out of defect, and there were no exceptions in all specimens of the BCP/CCP group. This indicates that the plasticity and adhesiveness of CCP may help to stabilize graft particles, functioning like a membrane or fixation screw in defects, preventing soft-tissue collapse. However, the amount of new bone formation in the BCP/CCP group was lower than that observed in the BCP/ACS group after either 4 or 8 weeks of healing. Moreover, histologic specimens from the BCP/CCP group appeared similar to those from defects filled with only CCP. In the former there were multinucleated giant cells and inflammatory cells around the BCP particles, as well as a minimal amount of immature woven bone. In the BCP/CCP group, CCP certainly played a role as a mechanical binder, but did not demonstrate a synergistic effect in terms of new bone formation.

Although the CCP and BCP/CCP group exhibited limited new bone formation compared to the BCP/ACS group, it was found that the augmented areas of the former were well maintained over the entire healing period, again without soft-tissue collapse. These observations suggest that CCP may be an effective defect filler for an atrophied alveolar ridge, or for large osseous defects such as cystic cavities, if biocompatibility and osteoconductivity of CCP were improved.

In conclusion, CCP resulted in limited new bone formation in rabbit calvarial defects throughout the healing period, attracting inflammatory cells that were observed histologically. However, its placement into bone defects demonstrated its ability to stabilize graft particles and to maintain augmented areas. Future investigations should attempt to improve the biocompatibility and osteoconductivity of CCP.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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