

The Effect of Recombinant Human Bone Morphogenetic Protein-2/Macroporous Biphasic Calcium Phosphate Block system on Bone Formation in Rat Calvarial Defects

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I. INTRODUCTION

The use of autogenous bone grafts have been considered to be the gold standard for new bone formation. Currently, the use of block shaped bone grafts is a well-accepted procedure in oral and maxillofacial rehabilitation^{1,2)}. However, autogenous grafting has limitations including inadequate supply and surgical morbidity, as well as donor site pain and infection. Moreover, significant volumetric resorption of the graft poses a clinical problems in the case of block grafts from endochondral donor sites³⁾. Therefore, an alternative biomaterial to autogenous bone is needed.

Since Urist discovered bone morphogenetic

proteins (BMPs)⁴⁾, more than 20 BMPs have been identified with several BMPs, such as BMP-2, -4, -5, -6, and -7, being reported to have significant osteoinductive activity⁵⁻¹⁰⁾. Accordingly, there have been many trials using rhBMPs for bone tissue engineering. The implantation of BMPs alone does not induce bone formation because the protein rapidly diffuses from the site of implantation. Therefore, many studies have been carried out with the aim of identifying an ideal carrier system for rhBMPs.

For clinical success using rhBMPs, the carrier should be easy to manipulate and be made into a specific shape. It also needs to provide sufficient firmness against soft tissue pressure during the healing period. Therefore,

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the ability to predict the volume and shape of regenerated bone is essential.

To date, studies of such carriers include biological materials such as bone matrix¹⁰, absorbable collagen sponge (ACS)¹¹⁻¹⁵, fibrin fibronectin sealing system (FFSS)¹⁶⁻¹⁸, synthetic polymers^{19,20}, β -tricalcium phosphate (TCP)^{11-13,18,21,22} and macroporous biphasic calcium phosphate (MBCP)^{23,24}.

Although various carriers for rhBMPs have been investigated, there is as yet no ideal carrier system available. In many cases, volumetric reduction of the rhBMP-induced bone has been reported^{13,14}.

MBCP is composed of 40% TCP and 60% hydroxyapatite (HA), which is considered to be an ideal mixture ratio for bone substitutes²⁶⁻²⁸, and has been reported to have favorable osteoconductive and osteoinductive properties²⁶⁻³¹. Volumetric reduction was reported to be considerably low due to its relatively low resorption rate²⁷⁻²⁸. Therefore, the block shape of the MBCP might be a suitable carrier for predictable bone formation in terms of the volumetric stability.

The aim of this study was to determine the osteogenic effect of an MBCP block as a carrier system for rhBMP-2 using a rat calvarial defect model.

II. MATERIALS AND METHODS

1. Animals

Thirty-two male Sprague-Dawley rats (weight

250~300 g) were used. The rats were maintained in plastic cages in a room with a 12 h-day/night cycle and an ambient temperature of 21°C, with access to water and standard laboratory pellets ad libitum. Animal selection and management, surgical protocol, and preparation were in accordance with the routines approved by the Institutional Animal Care and Use Committee, Yonsei Medical Center, Seoul, Korea.

2. rhBMP-2 Implant Construction

Disc-shaped MBCP implants (Biomatlante, Vigneux de Bretagne, France) (3mm height and 8mm diameter) were manufactured. rhBMP-2 (R&D Systems Inc., Minneapolis, MN, USA) was reconstituted and diluted in a buffer to a concentration of 0.025 mg/ml. For the rhBMP-2/MBCP implants, the MBCP implants were loaded with 0.2 ml of the rhBMP-2 solutions for one hour before surgery. For the MBCP implants, the MBCP implants were loaded with 0.2 ml of a buffer solution (Figure 1).

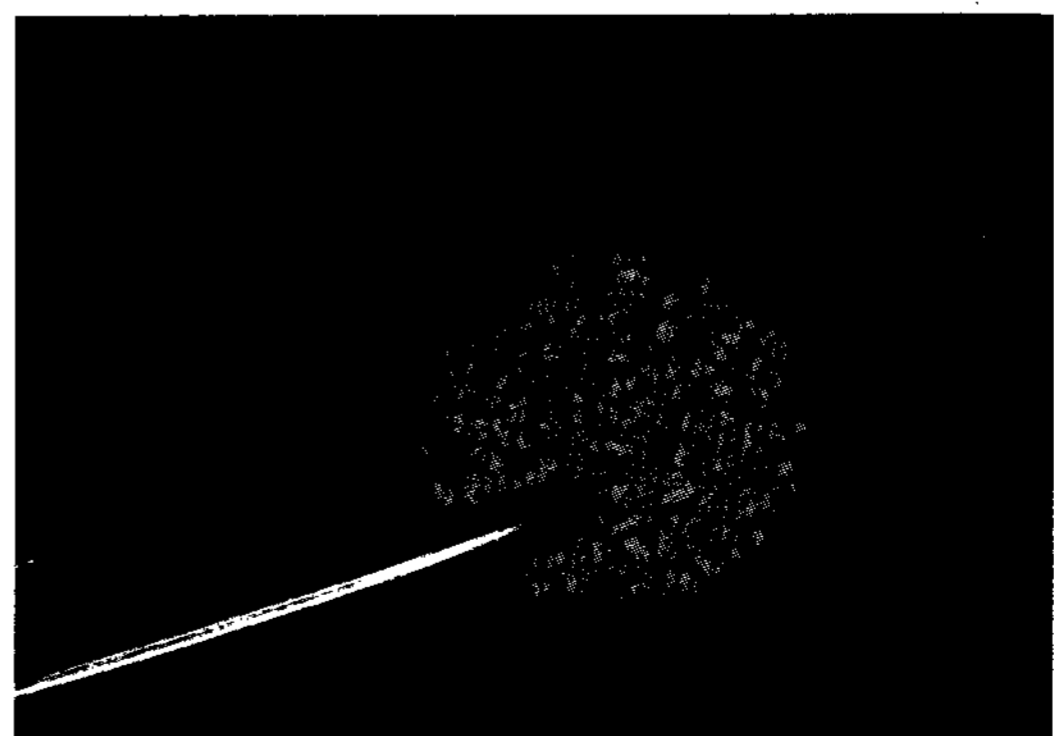


Figure 1. Block type MBCP implant used in this study.

3. Surgical Procedures

The animals were anaesthetized by an intramuscular injection (5 mg/kg body wt.) of a 4:1 solution of ketamine hydrochloride Ketalar[®] (Yuhan Co., Seoul, Korea):Xylazine, Rompun[®] (Bayer Korea, Seoul, Korea). Routine infiltration anaesthesia, 2% lidocaine, 1:100,000 epinephrine (Kwangmyung Pharm., Seoul, Korea) was used at the surgical site. An incision was made in the sagittal plane across the cranium and a full thickness flap was reflected to expose the calvarial bone. A standardized, circular, transosseous defect, 8 mm in diameter, was created on the cranium using a saline-cooled trephine drill (3i, Palm Beach Gardens, FL, USA). The animals were divided into 2 groups containing 16 animals each and allowed to heal for 2 (8 rats) or 8 weeks (8 rats). Each animal received 1 of the 2 experimental treatments: MBCP carrier control and rhBMP-2/MBCP. The periosteum and skin were closed and sutured with an absorbable monofilament suture, Monosyn[®] (Aesculap AG Co. KG., Tuttlingen, Germany) for primary intention healing.

4. Histology and Histometric Procedures

Two and 8 weeks after surgery, the animals were sacrificed by CO₂ asphyxiation. The block sections, including the experimental sites, were removed and fixed in a 10% neutral buffered formalin solution for

10 days. The samples were decalcified using 5% formic acid for 14 days and embedded in paraffin. Serial sections, 7 μ m thick, were prepared at 80 μ m intervals, stained with hematoxylin/eosin (H-E), and examined by optical microscopy. The most central sections from each block were selected for the histology and histometric evaluation.

The computer-assisted histometric measurements were obtained using an automated image analysis system coupled with a video camera attached to an optical microscope. The sections were examined at magnifications of $\times 20$ and $\times 100$. The histometric parameters were defined as follows (Figure 2).

- Augmented area (mm²): all tissues within the boundaries of the MBCP carrier, i.e. new bone, fatty marrow, fibrovascular tissue/marrow and residual biomaterial.
- New bone area (mm²): the area of newly formed bone within the total augmented area.

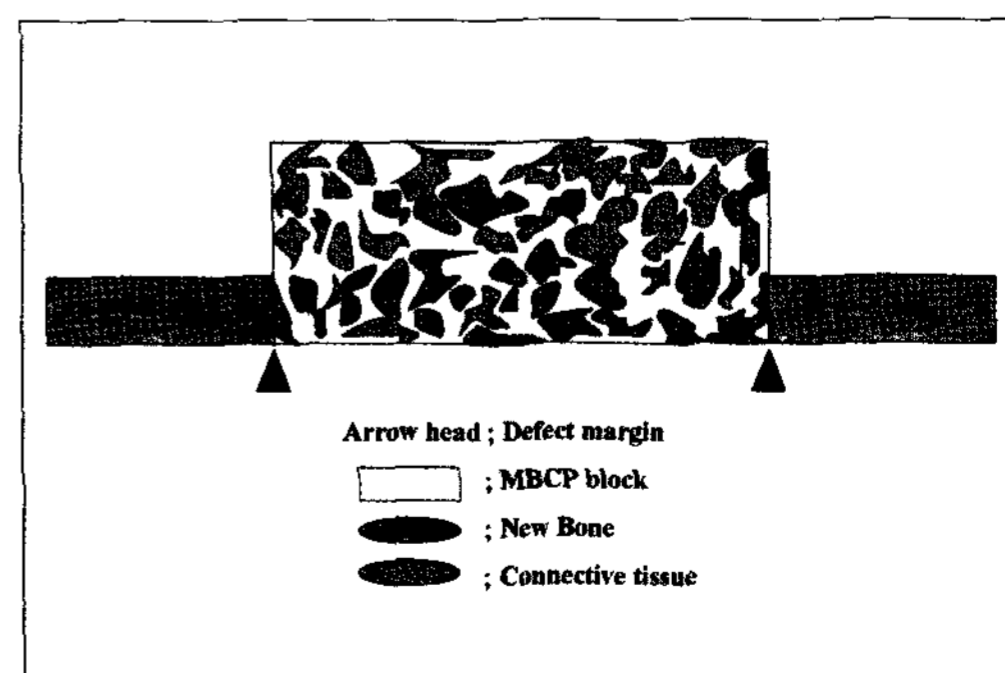


Figure 2. Schematic diagram of the calvarial osteotomy defect showing histometric analysis.

5. Statistical Analysis

The histometric recordings from the samples were used to calculate the means and standard deviations (mean \pm SD). The interactions between the healing interval and treatment condition were examined using a two-way analysis of variance (two-way ANOVA). A paired or unpaired t-test was used for the comparisons between the two groups. A p-value <0.05 was considered significant.

III. RESULTS

1. Histology Observations

1) MBCP control group (Figure 3).

At 2 weeks, there were generally no histological markers of inflammation or foreign

body reactions found. A small amount of new bone formation was observed adjacent to the margins of the defect and beneath the MBCP block. Evidence of osteogenic activity, such as a dense osteoblast-like cell lining, osteoid and bone apposition along the surface of the macropores in the lower part of the implant was observed. Macropores in the upper part were usually filled with loose fibrous connective tissue and the bone-forming activity was rare.

At 8 weeks, the majority of macropores in the lower part of the block were filled with newly formed bone. The specimens showed a more advanced stage of remodeling and consolidation. Loose or dense fibrous connective tissue was observed in the central and upper part of the block.

There was no significant resorption of the MBCP block observed during the healing time.

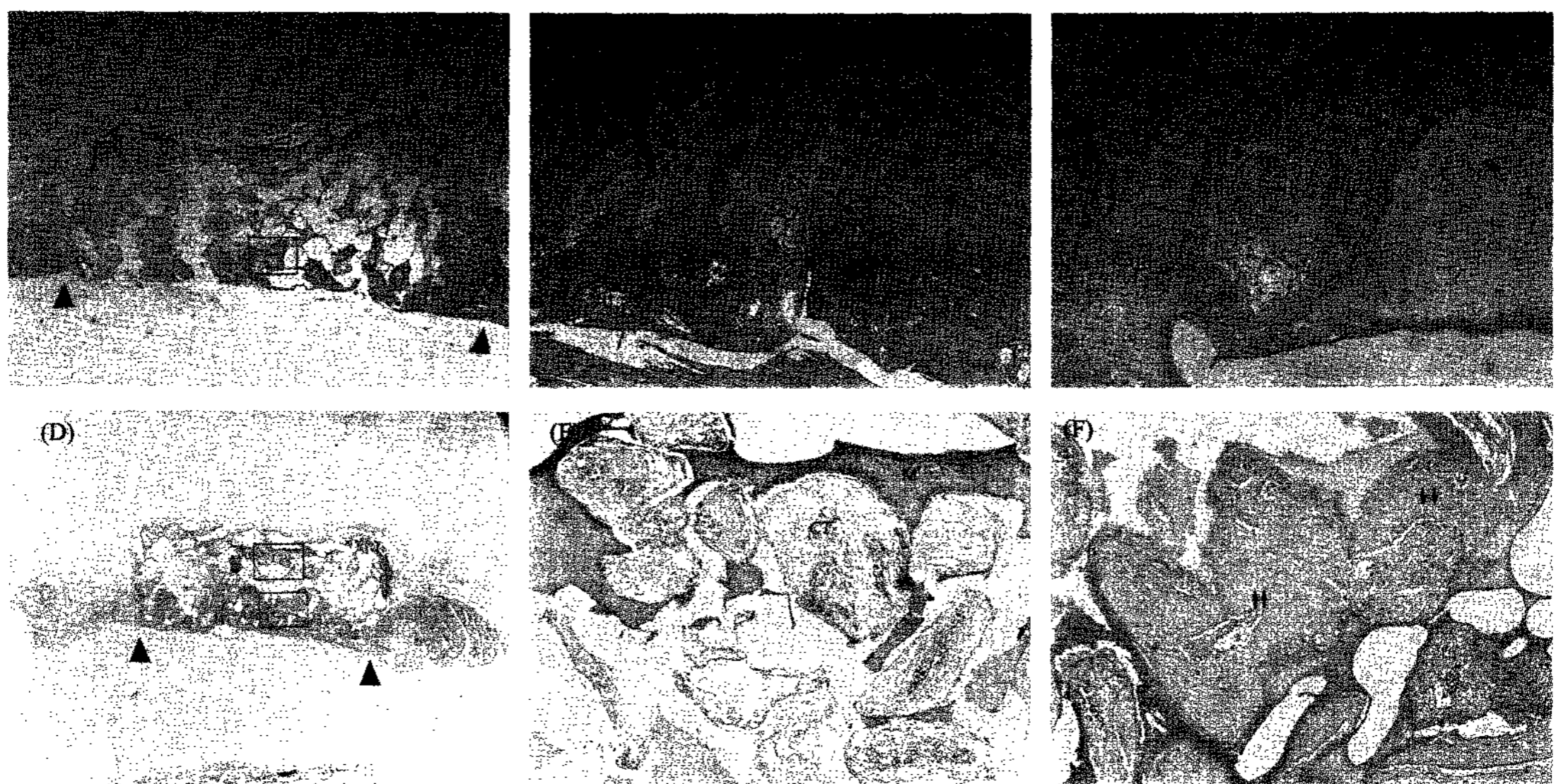


Figure 3. Representative photomicrographs of the MBCP control group at 2 (A,B and C) and 8 weeks (D,E and F) (arrow head: defect margin; arrow: cement lines, M;MBCP, NB: new bone, CT; connective tissue, H-E stain; original magnification A and D x20, B,C,E and F x100).

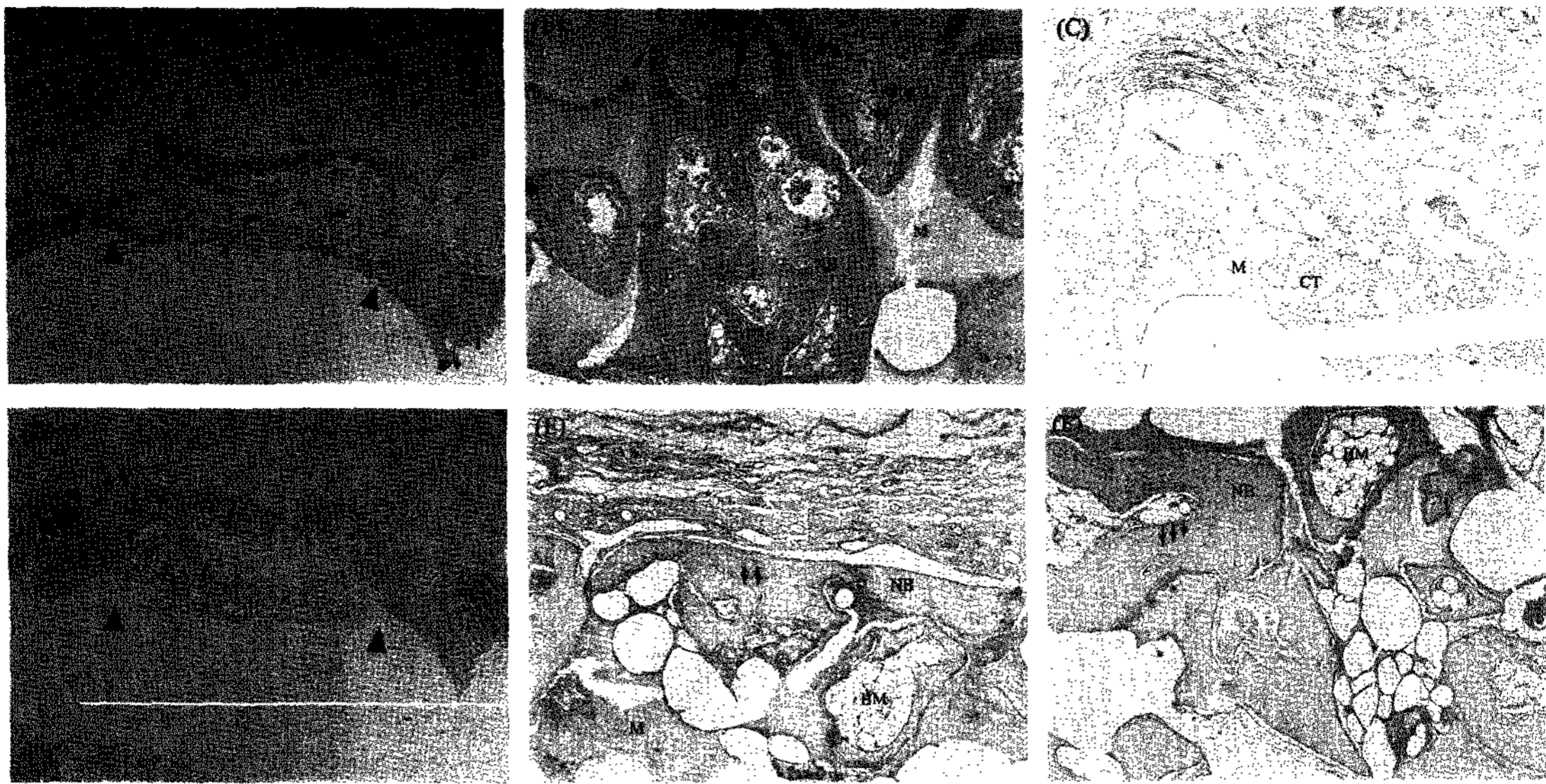


Figure 4. Representative photomicrographs of the rhBMP-2/MBCP group at 2 weeks (A,B and C) and 8 weeks (D,E and F) (arrow head: defect margin, arrow: cement lines, M;MBCP, NB: new bone, CT; connective tissue, BM;bone marrow, H-E stain; original magnification A and D x20, B,C,E and F x100).

2) MBCP/ rhBMP-2 group (Figure 4).

At 2 weeks, the overall bone healing was similar to that of the MBCP control group. The majority of macropores in the lower part of the block were filled with new bone. Beneath the block, the defect sites were almost completely bridged with new bone. However, there was little bone forming activity in the central and upper part of the block. In the case of macropores with bone forming activity, new bone that was associated cement lines was in direct contact with the surface of the MBCP, and an osteoblast-like cell lining was observed in the center area suggesting that bone formation and mineralization proceeded inwards from the implant surface.

At 8 weeks, the quantity of new bone beneath the block and macropores in the lower part of the block was greater than that ob-

served at 2 weeks, and the specimens showed a more advanced stage of remodeling and consolidation. Even though some macropores with fibrous connective tissue was noted in the central and upper part of the block, macropores with newly formed bone could be also found.

The newly formed bone consisted of woven and lamellar bone, and showed cement lines that were separated earlier from the more recently deposited bone. There was no evidence of cartilage formation. However, fatty marrow was observed in the central aspect of the newly formed bone.

2. Histometric Analysis

Tables 1 and 2 show the results of histometric analysis.

The new bone area in the rhBMP-2/

Table-1. Total augmented area (group means \pm SD, mm², n=8)

MBCP	20.5 \pm 3.5	20.3 \pm 2.7
rhBMP-2/MBCP	22.4 \pm 3.4	21.5 \pm 1.8
No significant difference when compared to all groups (P>0.01)		
8 Weeks		
MBCP	1.1 \pm 0.6	3.0 \pm 0.9*
rhBMP-2/MBCP	3.0 \pm 0.9 [†]	5.5 \pm 2.2 ^{*†}

* : Statistically significant difference compared to 2 weeks (p < 0.01)

[†] : Statistically significant difference compared to MBCP group (p < 0.01)

MBCP group were significantly larger than in the MBCP group at each healing interval (p <0.01). In both groups, the quantity of the new bone was greater at 8 weeks than at 2 weeks (p <0.01). Two-way ANOVA revealed that the time had a significant effect on new bone formation in both groups (P<0.01). However, the pattern of the changes in bone healing over time was not significantly different.

IV. DISCUSSION

This study examined the osteogenic effect of a MBCP block as a carrier system for rhBMP-2 using a rat calvarial defect model. The results after a 2- and 8-week of healing period were evaluated by the histology and histometric parameters. The rationale behind this was to utilize the favorable bone healing capacity of MBCP block, which is known to have osteoconductive and osteoinductive effect, and to have volumetric predictability over healing time because of low resorption rate and resistance of block

type against to soft tissue compression. It was expected that the rhBMP-2 using MBCP block would result in predictable new bone formation in terms of volume and shape.

rhBMPs have been shown to have potent osteoinductive activity^{4-6,13)} and there have been many trials using rhBMPs in bone tissue engineering⁷⁻²³⁾. Hence, bone tissue engineering technology might be an alternative to autogenous bone graft. The results of bone tissue engineering using rhBMPs are fully dependent on the characteristics of the carrier systems as biomaterials. Therefore, many biomaterials have been evaluated as a carrier system for rhBMPs.

In this study, MBCP alone produced favorable bone healing. Although limited bone formation was observed in the middle and upper part of the block, new bone was observed homogeneously in the lower part of the block. Almost complete defect closure beneath the block was observed and the majority of the macropores in the lower part of the block were filled with newly formed

bone after 8 weeks in MBCP block alone group. These results are comparable to previous studies using other biomaterials such as TCP granules^{11,12,21)}, FFSS^{17,18)}, and ACS^{9,11)}, where complete defect closure had not been achieved. Defect closure did not exceed 30-35% of the defect width after implanting these biomaterials. The favorable bone healing effects of MBCP might explain the complete defect closure observed in this study.

The favorable osteoconductive effect of the MBCP in bone healing is well documented²⁵⁻²⁸⁾. It was suggested that higher local calcium and phosphate concentrations in MBCP might have had a stimulatory effect on bone formation. In addition to the osteoconductive effect of MBCP, there are many reports on the osteoinductive effect of MBCP when implanted in ectopic sites in various species²⁹⁻³²⁾. Ectopic bone formation could be also observed using other type of synthetic bone substitute such as hydroxyapatite. However, MBCP was reported to have a higher osteoinductive potential²⁹⁾.

Synthetic biomaterials with a porous structure such as MBCP have been reported to entrap rhBMPs within its pores, and intrinsically diffusible rhBMPs can be retained and their activity prolonged²²⁾. It is believed that the porous structure of MBCP allows cells and newly formed tissues to migrate into the block. New bone formation in the macropores of the MBCP block in this study can explain this phenomenon. Ectopic bone formation around the MBCP was also reported when rhBMP were implanted with MBCP in

the rat subcutaneous model²⁴⁾. Therefore, the MBCP block could be recommended as a carrier for rhBMPs.

In a clinical point of view, a carrier for the delivery of BMPs should serve as a scaffold for bone forming cells while providing a space in which bone formation can occur. In addition, the space should be maintained for a relatively long period in order to allow sufficient maturation of the newly formed bone. In terms of clinical bone tissue engineering, the provision of the volume and shape of the bone tissue is a key factor in treatment success.

When rhBMPs was impregnated with biomaterials as a carrier, some of which include ACS¹¹⁻¹³⁾, β -TCP^{11-13,18,21)} and FFSS^{17,18)}, they induced excellent new bone formation. However, the amount of newly formed tissue was reduced at a later healing stage compared with at an earlier stage because of soft tissue compression during the healing periods. When implanted at an ectopic site such as a subcutaneous pouch, the new bone induced by rhBMP-2/ACS at two weeks could not be observed at eight weeks, while more expanded bone maturation was observed in the rhBMP-2/ β -TCP sites during that same period¹³⁾. Moreover, ACS was not effective as a carrier for rhBMP-2 on ridge augmentation in chronic alveolar ridge defects in dogs, which was attributed to a non space-providing defect due to soft tissue compression during the healing period¹⁴⁾. The lack of space-providing capacity of ACS was suggested to be a major factor re-

sponsible for its failure to maintain the newly induced bone. Although particle types such as β -TCP can serve as an effective carrier for rhBMPs, there are questions as to whether clinical applications are possible because the nature of the particulate form creates difficulties regarding its manipulation for the intended shape of bone. Since predictable bone tissue regeneration could be one of the major clinical therapeutic goals, a carrier system for rhBMPs needs to provide stability over the time in terms of volume and shape.

In this study, the total augmented area was stable during the healing periods in two groups. As reported earlier, MBCP is composed of 40% TCP and 60% HA^{26,27,30}. The higher TCP content in MBCP suggests that it would be resorbed. However, there was no decrease in size or change in shape related to resorption. Moreover, there was no active resorption phenomenon observed on histology findings at 8 weeks. It was reported that there was no significant resorption with decreases in size with a longer healing time using other species^{26,29}. These results suggest that a MBCP block could serve as a carrier system for predictable bone tissue engineering using rhBMPs. In particular, the rhBMPs/MBCP block system is recommended for bone tissue reconstruction in oral and maxillofacial areas, in which a characteristic 3-dimensional topography and soft tissue compression during the healing periods are important consideration factors.

V. CONCLUSION

The block type of MBCP as a carrier for rhBMP-2 is effective in new bone formation. The total augmented area induced by the rhBMPs/MBCP block system was stable during the observed healing period. These results suggest that the rhBMPs/MBCP block system can be used for predictable bone tissue reconstruction

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백서 두개골 결손부에서 bone morphogenetic protein-2의 전달체로서 macroporous biphasic calcium phosphate-block의 골재생요과

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골형성 유도 단백질(bone morphogenetic protein, BMP)은 성장이나, 골형성과정에서 중용한 역할을 한다고 입증되었고 그것의 운반체에 대한 연구가 이뤄져 왔다. 하지만 수직압이 존재하는 곳에서 골증대술에 적용할 수 있을 만큼 강한 공간유지능력이 있는 운반체에 대한 연구는 그리 많지 않았다. Macroporous biphasic calcium phosphate block (MBCP block)은 공간유지능력이 뛰어나며 강한 수직압을 견딜수 있는 골대체물질이다. 이 연구의 목적은 MBCP block을 골형성유도 단백질(rhBMP-2)의 운반체로 사용하여 백서 두개골 결손부에 적용하였을 때, 골 형성 효과를 평가하는 것이다.

36마리의 웅성백서에서 8mm 지름을 갖는 임계크기의 두개부 결손을 형성하였다. 20마리씩 2개의 군으로 나누어 MBCP block만 이식한 군, MBCP block을 운반체로 사용하여 농도 0.025mg/ml rhBMP-2를 이식한 군으로 나누어 술 후 2주와 8주에 치유결과를 조직학적, 조직계측학적으로 비교 관찰 하였다.

조직계측학적 관찰 결과, rhBMP-2/MBCP block 군에서 MBCP block군에서 보다 2, 8주 모두 골밀도(bone density)가 유의성있게 증가하였다 ($P<0.01$). 각 군에서도 8주째가 2주째보다 골밀도가 유의성있게 증가하였다($P<0.01$). 총조직 형성량 (augmented area)에서는 변화가 없었다. 이 연구 결과, 백서 두개골 결손부에서 MBCP block은 rhBMP의 운반체로 사용하였을 때 신생골 형성에 유의한 효과가 있을뿐 아니라 공간유지능력이 우수해서 수직압이 존재하는 골증대술(bone augmentation)시 rhBMP의 운반체로 가능성이 있다고 사료된다.