Histologic and clinical evaluation of maxillary sinus augmentation using macroporous biphasic calcium phosphate in humans

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연구 내내 많은 관심과 도움을 주셨던 방은경 선생님, 윤정호 선생님과 치주과 의국원들, 그리고 3년 동안 한솥밥 먹으며 동고동락한 수련 동기들에게 깊은 감사와 애정을 전합니다.

그리고, 늘 조건 없는 사랑을 주시고 말없이 저를 믿어 주시는 사랑하는 부모님과 언니에게 진정으로 사랑과 고마움의 마음을 전합니다. 모든 분들께 진심으로 감사드립니다.

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Table of Contents

List of Figures

List of Tables

Abstract

Histologic and clinical evaluation for maxillary sinus augmentation using macroporous biphasic calcium phosphate in humans

Several bone grafting materials have been used in sinus augmentation procedures. Macroporous Biphasic Calcium Phosphate (MBCP) consists of the mixture of 60% HA and 40% β-TCP. Therefore, it can provide good scaffold for the new bone to grow owing to HA, in the other hand, it can have bioactivity for bone remodeling owing to β-TCP. The purpose of this study was to evaluate bone formation following maxillary sinus augmentation using MBCP by means of histologic analysis.

MBCP was placed as a primary bone substitute for maxillary sinus augmentation. 35 patients were selected after evaluation of their medical and dental examination and devided into three groups. MBCP only, MBCP combined with Irradiated cancellous bone and MBCP combined with autogenous bone were used for each group. After average 6.83 months, bone biopsies were harvested for histologic evaluation and total 80 fixtures were installed.

All patients were followed during 15.32±3.88 months in average after sinus floor augmentation surgery. All fixtures showed good initial stability but 1 fixture was removed during follow-up period. Histologic evaluation revealed that individual MBCP particles were partially infiltrated or surrounded by blood vessels and newly-formed bone. New bone was characterized by abundant marrow, basophilic reversal line and lacunae containing osteocytes. Histometrically, there was no significant difference between groups in the amount of newly-formed bone.

These results documents that MBCP when used as a grafting material for sinus floor augmentation whether combined other bone graft material or not, may lead to the predictable results for dental implants on posterior maxillary area with insufficient vertical height for fixture installation.

Key Words: dental implant; macroporous biphasic calcium phoasphate; irradiated cancellous bone and marrow; maxillary sinus augmentation; comparison study; bone regeneration

Histologic and clinical evaluation of maxillary sinus augmentation using macroporous biphasic calcium phosphate in humans

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I. Introduction

Maxillary sinus augmentation is an established method intended to achieve sufficient vertical bone height on the maxillary posterior region prior to the placement of endosseous dental implant. This technique was first published in 1980 by Boyne and James[5] and subsequently developed and modified by other clinicians[30,39].

Although this procedure has become routine for the patient who has insufficient bone height on maxillary posterior region for implant placement, the question of what the best bone substitute to be used to filled in the sinus cavity is, has not been answered.

It has been preferred to use autogenous bone from various donor sites for the sinus floor augmentation[2,5,23,24, 39]. Even though autogenous bone is considered as gold standard, in recent years, some researchers have demonstrated the stability and effectiveness of the mixture of hydroxyapaptite (HA) and beta-tricalcium phosphate (β-TCP) as bone graft material for bone regeneration. While HA provides a good scaffold for the new bone to grow, it has been shown to have poor regeneration potential, β-TCP has been proven to form new bone within the periodontal osseous defects whereas their resorption pattern and rate was found to be unpredictable[6,7,11,17]. Therefore, the judicious mixing of a stable component (HA) and a more bioactive component (β-TCP) involves controlled bioactivity and a perfect equilibrium between ceramic resorption and bone substitution[25,40].

There are many studies carried out to decide the most proper ratio of HA/β-TCP. Some researches have shown that higher HA ratio causes accelerated new bone formation in osseous defects.[18,25] According to studies conducted by Nery, LeGeros[25] in the United States, Daculsi[6,7] in France, the mixture of 60% of HA and 40% β-TCP constitutes an ideal mixture for biphasic calcium phosphate ceramics as a bone substitute. Macroporous biphasic calcium phosphate (MBCP) is presented in a porous form required for the biological exchanges particularly for bone ingrowth and mineralization.[11]

The recent reports that HA or β-TCP[27], even without autogenous bone, could be a satisfactory graft and have comparable results to autogenous bone graft. In spite of these results, it has been anticipated that the addition of autogenous bone or osteoinductive materials such as DFDBA, FDBA will induce and facilitate bone formation with corporation of the bone graft materials. For those reasons, in this study irradiated cancellous bone and marrow (ICB) was used, which is known as frozen, irradiated allogenic vertebral bone. It is believed that the irradiation used to eliminate the antigenicity of donor does not eliminate the osteoinductive and osteoconductive element of the graft

The aim of this study was to evaluate bone formation following maxillary sinus augmentation using MBCP, mixture of MBCP and ICB, and mixture of MBCP and autogenous bone by means of clinical and histologic analysis.

Ⅱ. Materials & Methods

1. Study populations

Thirty five patients (9 females, 26 males) who have the insufficient residual bone height (less then 5 mm) were selected. Their ages ranged from 30 to 73 years, with a mean of 51 years. The inclusion criterion was that less than 6 mm of alveolar bone in the floor of the sinus remained, as determined by computed tomography[42]. All patients were neither involved in any contraindication of dentoalveolar flap surgery, nor in maxillary sinus problems, such as a recent history of acute maxillary sinusitis. In 25 patients, a 2-stage approach was performed. In 10 patients with bone height to make it possible to get initial stability (4 to 6mm), a 1-stage approach was performed[42]. A total of 80 implants were inserted (Table 1-3). 47 were oxidized titanium screw type implants[#] and 33 were sand-blasted, large grit, acid-etched solid screw type implants[$]. Only 2 patients were bilaterally edentulous; the remaining patients were unilaterally edentulous.

2. Sinus Floor Augmentation Technique

All surgical procedures were completed under local anesthesia[§]. Mucoperiosteal flap was reflected for good access to the lateral sinus wall. Then, a sinus window was outlined using diamond round bur under continuous cooling using sterile saline. A green-stick fracture was induced using an osteotome and mallet, the infracture sinus lateral wall is rotated medially and the Schneiderian membrane was dissected dedicatedly (Fig 1b). Care was taken not to perforate the membrane.

The produced cavity was filled with the graft material under meticulous condensation (Fig 1c). The defect of the lateral wall was covered with a collagen membrane, Collatape[||] (Fig 1d). Mucoperiosteal flap is repositioned over the collagen membrane and sutured for primary closure with 5-0 coated Vicryl[¶] and 4-0 Monosyn[**] .

After 6 to 10 months (average 6.73 months) following the augmentation procedure in the patients who 2-stage procedure was performed, fixtures of 4 or 5mm in diameter were installed. At the same time, a lateral biopsy for each side was taken cranially from the dental implant by use of a hollow trephine drill[††] (Fig 2b). All dental implants installed presented good initial stability. The sequences of surgery were presented in figure 1 and 2.

3. Bone augmentation materials

The patients were divided into 3 groups: 14 patients received MBCP only for sinus floor augmentation (Group I), another 15 patients received MBCP[*] combined with ICB[†] (proportion 50:50) (Group II) and the other 8 patients received MBCP combined with autogenous bone (proportion 80:20) for sinus floor augmentation (Group III). The corticocancellous bone of mandibular ramus or maxillary tuberosity was harvested for autogenous bone graft (Table 3). The autogenous block bone harvested from the mandibular ramus using trephine drill was particulated with bone crusher[##]. It was with bone rongeur[$$] that autogenous bone was harvested from maxillary tuberosity.

4. Histologic processing and histomorphometric analysis

After the biopsies were taken, they were immediately fixed in 10% buffered formalin for 10 days. After rinsing in water, the sections were decalcified in 5% formic acid for 14 days and embedded in paraffin. Serial sections, 5 um thickness were cut on longitudinal plane. From each bone core, the central section was selected and stained with hematoxylin and eosin (H&E) and examined using light microscopy coupled to a video camera[¶¶] which can take a picture of the slide and save as a figure file.

The slides were coded so that the examiner who performed the histometric analysis was blind to the treatment. Following parameters were measured using Image-pro program[§§] semiautomatically. The surface of the bone substitute particles and newly formed bone was marked using the cursor. The nature of the surface could thus be automatically calculated by counting the number of pixels.

(1) Vital bone surface

(2) Marrow and connective tissue surface

(3) Remaining particle surface

[#] TiUnite™, Nobel Biocare, Göteborg, Sweden

[$] SLA ; Sand-blasted, large grit, acid-etched, ITI dental implant system, Straumann, Switzerland

* MBCP™ Biomatlante Sarl, France

† Irradiated cancellous bone and marrow, Rocky mountain tissue bank, USA

[##]Bone crusher, stainless steel. G. Hartzell & Son., Inc, Germany

[$$] Beyer double action rongeur, ACE surgical supply Co., Inc. USA

§ 2% lidocaine, 1:100,000 epinephrine, Kwangmyung Pharm., Seoul, Korea

‖ Collatape®, Calcitek, Carlsbad, CA, USA

¶ Polyglactin 910, braided absorbable suture, Ethicon, Johnson & Johnson Int., Edinburgh, UK

** Glyconate absorbable monofilament, B-Braun, Aesculap,INC.,USA

†† 3i, West Palm Beach, FL, USA

§§ Image-Pro Plus®, Media Cybernetics, Silver Spring, MD, USA

¶¶ Olympus BX50, Olympus Optical Co., Tokyo, Japan

Ⅲ. Results

1. Clinical observations

All augmented sinuses healed well and none of all patients had complications influential on prognosis of implants such as infection, maxillary sinusitis, and severe sinus membrane perforation. At the time of reentry surgery for fixture installation, the regenerated tissue in the window area showed a good consistency and was well-blended with adjacent host bone that the boundaries of osteotomy could not be distinguished from adjacent host bone easily in all of the 3 groups (Fig 2a). The fixtures in the 21 patients were uncovered simultaneously with installation of them because of excellent initial stability (Fig 2b). After a healing period of 6 months, abutment connection was performed in the other patients. All patients were followed during 15.32±3.88 months in average after sinus floor augmentation surgery. 18 patients were completed with prosthetic treatment with screw-retained or cemented-type fixed prostheses in follow-up period.

Only one fixture was removed so far, which belonged to Group III and was explanted one month after installation surgery. The failed implant was replaced by wider fixture (SLA solid screw type implant) successfully (Table 3).

2. Histological observations and Histomorphometric analysis

Histologic evaluation at the time of fixture installation revealed new bone formation in company with resorption of graft particles. Almost all particles of MBCP were embedded in or surrounded by newly formed bone and it was possible to observe a close contact between graft particles and newly formed bone trabecules (Figs 4, 5, 6). Newly formed bone was characterized by lacunae containing osteoblast, which seemed to be osteocyte, and had abundant medullary space filled with a well-vascularized connective tissue with no histologic markers of inflammation (i.e., neutrophils and macrophage) or foreign body reaction. The new cancellous bone also exhibited incremental basophilic lines (Figs 4, 6).

Individual MBCP particles were characterized by purplish-white tone and they were partially infiltrated by blood vessels and penetrated by newly-formed bone. These observations confirm that the MBCP has osteoconductive property. Highly magnified view in light microscope showed that the boundary between MBCP particle and newly-formed bone was irregular and not concrete (Figs 4c, 6c). This suggests that the resorption of MBCP particle might occur with the apposition of new bone simultaneously. However, in spite of those observations and presumption, osteoclastic activity of MBCP is not proven on the light microscope and only very slow resorption rate of MBCP particles could be supposed because we could find the remnant of MBCP particles even in the histologic evaluation of biopsy harvested in 6 to 10 months after sinus floor augmentation.

ICB, used with MBCP in Group II, identified clear differences in comparison to natural bone in spite of their similar color. In the area of ICB, the osteocyte lacunae were empty and the lamellar layer or reversal line was not obvious and distinct (Fig 5).

Table 4 shows the results of the histomorphometric measurements of three groups. An average 26.94±15.30%, 29.37±9.20% and 30.44±3.59% of newly-formed bone was measured respectively, for Group I, II, III. The remaining MBCP particles on average for Group I, II, III, was 11.59±9.41%, 11.17±6.58% and 21.83±15.55% respectively. There were no remarkable differences between the groups (Fig. 7).

IV. Discussion

The development of surgical technique and grafting materials for sinus floor augmentation has made it possible for patients with severely resorbed posterior maxilla to have another viable treatment option rather than denture[5,10,24,33,34,39,42].

There are definitely many advantages of autogenous bone graft, such as predominant osteogenic property, histocompatibility, and elimination of disease transmission. On the other hand, harvesting enough amount of autogenous bone from extraoral donor site requires general anesthesia, hospitalization, a donor site operation, and increased time for operation, and recovery of patients[20,26]. For these reasons, alternative grafting materials has been investigated and many authors have reported various grafting materials.

In the recent years, many researches showed that bovine hydroxyapatite could be used for bone substitute for sinus floor augmentation[1,9,12,13,16,17,22,28,29,34,41]. Bovine hydroxyapatite has been evaluated as highly biocompatible to human oral hard tissues and has showed some favorable results in the histologic and histomorphometric studies[9,13,17,22,40]. However, the resorption rate of this material was so slow that it was not suitable for rapid new bone formation even though such characteristics could supply a good scaffold for bone regeneration[6,25].

In this study, macroporous biphasic calcium phosphate (MBCP) was evaluated histologically and clinically. MBCP was developed for a better control of the biomaterials resorption and bone substitution[4,6,7,19,40]. An optimum balance of the more stable phase of hydroxyapatite and more soluble tricalcium phosphate was obtained for controlling gradual dissolution in the body, seeding new bone formation as it releases calcium and phosphate ions into the biological environments[6]. MBCP consisting of 60% HA and 40% β-TCP, could maximize the advantages of each material.

Although there is some controversy in the literature as to whether such alloplasts allow enough bone formation by themselves for the fixation of dental implants, a good initial stability was achieved in all of 3 groups and made it possible to connect healing abutments or healing caps simultaneously with fixture installation in the 21 of 35 patients. It was made possible to overcome the poor bone quality (type III or IV) through well-known method such as drilling with smaller one than optimum drill, and bone compaction using osteotome.

In spite of these findings, one fixture in Group III was removed at one month after fixture installation surgery and simultaneous uncovering procedure. It is suspected that the most distal implant went through premature loading after surgery and it could make it possible that implant with good initial stability was lost in one month.

While only MBCP was used in the group I, MBCP was combined with autogenous bone or irradiated cancellous bone and marrow, which are known as grafting material with osteogenic or osteoinductive properties in other 2 groups. Histologically and histomorphometrically, regardless of combination or not, newly formed bone was found on all specimens. And there were no remarkable differences between 3 groups in aspect of vital bone proportion. However, the portion of residual MBCP particles in Group II was less than other groups consistently. Based on this observation, it is possible to assume that association with ICB could fasten the remodeling process i.e., resorption of MBCP particles and apposition of new bone. In group III, combined with 20% autogenous bone, the portion of residual MBCP particles was higher than other two groups. This findings could make it possible that the percentage of autogenous bone combined was too small to accelerate the remodeling procedure compared to group II.

In the study by Hallman et al.[13], the corresponding values for the bone area parameter were 37.7±31.3%, 39.9±8%, and 41.7±26.6% for autogenous bone, mixture of 20% autogenous bone/80% bovine hydroxyapatite (BH), and 100% BH, respectively. Compatible to this study, there were no significant differences between 3 group. Moy et al.[24] demonstrated that the biopsy cores harvested from augmented area contained 44.4% bone after grafting with hydroxyapatite (HA) granules and chin bone, 59.4% bone after grafting with chin bone alone. These studies documents that alloplastic materials could derive some results comparable to autogenous bone graft or combination with autogenous bone and that alloplastic materials acted as osteoconductors for new bone apposition.

In conclusion, it could be documented that MBCP when used as a grafting material for sinus floor augmentation whether combined other bone graft material or not, may lead to the predictable results for dental implants on posterior maxillary area with insufficient vertical height for fixture installation.

V. Conclusion

In order to evaluate sinus floor augmentation using MBCP histologically and clinically, a total of 35 patients and 37 maxillary sinuses were augmented with MBCP 100% (Group I), a mixture of MBCP 50% and irradiated cancellous bone and marrow (Group II), a mixture of MBCP 80% and autogenous bone 20% (Group III). Healing time was 6 to 10 months prior to fixture installation surgery in the case of the 2 stage approach. Bone biopsies from the trap door site were harvested for histologic evaluation at the time of implant placement. A total of 80 fixtures were place and followed up for 10 months after implant installation surgery.

1. 1 of the 17 implants placed in Group III was lost during follow-up period.
2. The short term clinical outcome and histologic and histomorphometric evaluation of the augmented area were found to be similar for maxillary sinuses after augmentation with MBCP, combination of MBCP and ICB, and combination of MBCP and autogenous bone.
3. MBCP whether combined with other material known as osteogenic or osteninductive materials, or not, was biocompatible and allowed osteoconduction.

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Legends

Figure 1. Sinus floor augmentation technique used in this study. a) Preoperative clinical view. b) The trap door is outlined and pushed inside. c) The produced cavity is filled with the mixture of MBCP and ICB. d) Sinus buccal window is covered with a collagen membrane, Collatape.

Figure 2. Clinical findings 6 months after surgery. a) Although the graft particle can be distinguished on the lateral wall, regenerated tissue in the window area is well-blended with adjacent host bone. b) Two fixtures are installed successfully. Bone biopsy is harvested from the previous trap door site using trephine drill.

Figure 3. Radiographic evaluations. a) Preoperative panoramic view. Vertical height of posterior maxilla is insufficient for implant insertion due to severe pneumatization. b) Six months after sinus floor augmentation. c) Six months after implant installation surgery.

Figure 4. Histologic finding 10 months after surgery (Group I). a) The MBCP particles are fully integrated into new bone and invaginated in woven bone (original magnification X100) b) Magnified view of a): grafted material (G) and vital bone (N) are in close contact and osteocytes are observed. The reversal line in newly formed bone is obvious (original magnification X400)

Figure 5. Histologic finding 6 months after surgery (Group II). a) Show the ICB characterized with empty lacunae, surrounded by newly-formed vital bone whose boundary is well-defined (arrow) (original magnification X100) b) Magnified view of a):osteoblastic cell lining (arrow head) and osteocytes in lacunae, which is the characteristics of vital bone (arrow) (original magnification X400).

Figure 6. Histologic findings 6 months after surgery (Group III). a) MBCP particles (G) embedded in newly-formed bone (N). Ample marrow space filled with loose connective tissue and abundant blood vessels (V) (original magnification X100) b) Magnified view of a) Irregular limit between the new bone and residual MBCP particle shows the progress of bone remodeling (arrow head), which ensures the replacement of grafted material (original magnification X400)

Figure 7. Results of Histomorphometric analysis. There were no remarkable differences between the groups for newly-formed bone surface.

Tables

Table 1. Patient Population Data (Group I)

Patient	Approach	N implants	Implant length	Implant type
1	2-stage	3	11.5,11.5,11.5	Oxidized titanium screw type
2	2-stage	3	13,13,13	Oxidized titanium screw type
3	2-stage	2	10,10,10	SLA solid screw type
4	2-stage	2	11.5,13	Oxidized titanium screw type
5	2-stage	2	11.5,13,13	Oxidized titanium screw type
6	2-stage	3	13,13,13	Oxidized titanium screw type
	2-stage	3	13,13,13	Oxidized titanium screw type
7	1-stage	2	10,10	SLA solid screw type
8	2-stage	3	10,10,10	SLA solid screw type
9	2-stage	2	12,12	SLA solid screw type
10	1-stage	2	12,12	SLA solid screw type
11	1-stage	2	11.5,11.5	Oxidized titanium screw type
12	2-stage	1	10	SLA solid screw type
13	1-stage	2	10,10	SLA solid screw type

Table 2. Patient population data (Group II)

Patient	Approach	N implants	Implant length	Implant type
1	1-stage	3	11.5,13,10	Oxidized titanium screw type
2	2-stage	2	13,13	Oxidized titanium screw type
3	2-stage	2	11.5,11.5	Oxidized titanium screw type
4	2-stage	2	12,12	SLA solid screw type
5	2-stage	1	14	SLA solid screw type
	2-stage	1	12	SLA solid screw type
6	2-stage	2	11.5,13	Oxidized titanium screw type
7	2-stage	2	12,12	SLA solid screw type
8	1-stage	2	11.5,11.5	Oxidized titanium screw type
9	2-stage	3	13,13,13	Oxidized titanium screw type
10	2-stage	3	14,12,12	SLA solid screw type
11	2-stage	2	12,12	SLA solid screw type
12	1-stage	2	11.5,11.5	Oxidized titanium screw type
13	2-stage	3	10,12,12	SLA solid screw type
14	2-stage	1	10	SLA solid screw type

Table 3. Patient population data (Group III)

Patient	Approach	N implants	Implant length	Implant type
1[#]	1-stage	3	13,11.5,10	Oxidized titanium screw type
2[†]	2-stage	2	13,12	1 oxidized titanium screw type, 1 SLA solid screw type
3[#]	1-stage	2	11.5,13	Oxidized titanium screw type
4[#]	2-stage	2	11.5,11.5	Oxidized titanium screw type
5[*†]	2-stage	2	10,10	1 oxidized titanium screw type, 1 SLA solid screw type
6[†]	1-stage	2	11.5,11.5	Oxidized titanium screw type
7[†]	2-stage	2	14,12	SLA solid screw type
8[†]	2-stage	2	11.5,11.5	Oxidized titanium screw type

* This patient went through explantation of region #27 one month after installation surgery. Two months after removal of fixture, the fixture of wider diameter was installed successfully.

[#] Autogenous bone was harvested from the mandibular ramus.

[†] Autogenous bone was harvested from the maxillary tuberosity.

Table 4. Results of Histomorphometric Analysis (Average±S.D.)

	New Bone (%)	Residual Graft Particle (%)	Soft tissue & Marrow (%)
MBCP 100% (n=6)	26.94±15.30	11.59±9.41	61.47±17.36
MBCP 50%+ICB 50% (n=9)	29.37±9.20	11.17±6.58	54.78±9.05
MBCP 80%+Auto 20% (n=4)	30.44±3.59	21.83±15.55	47.72±18.26

Figures

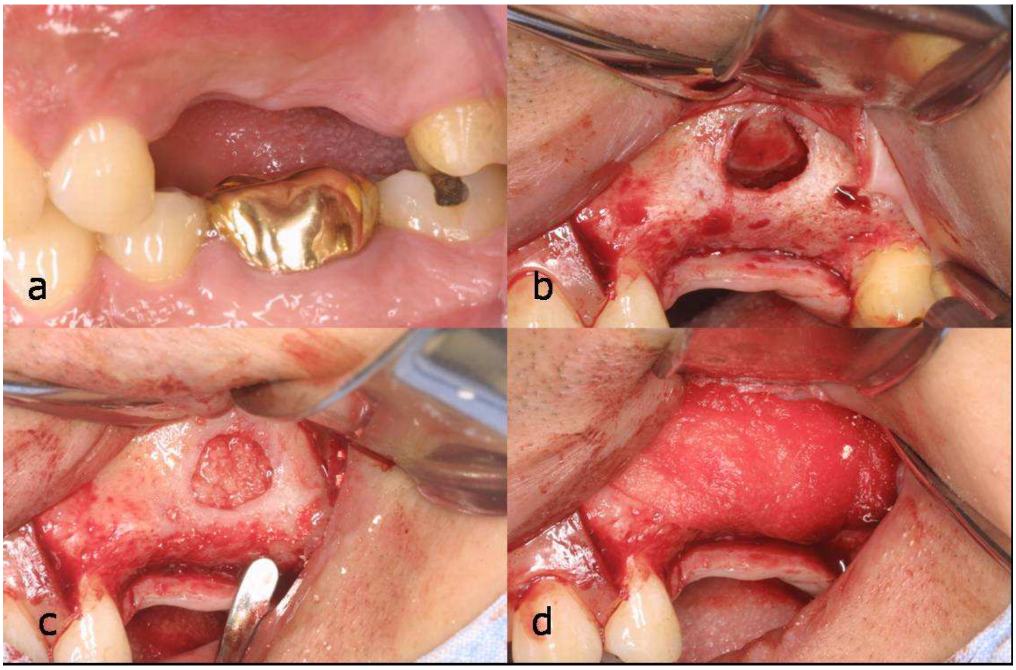

Figure 1

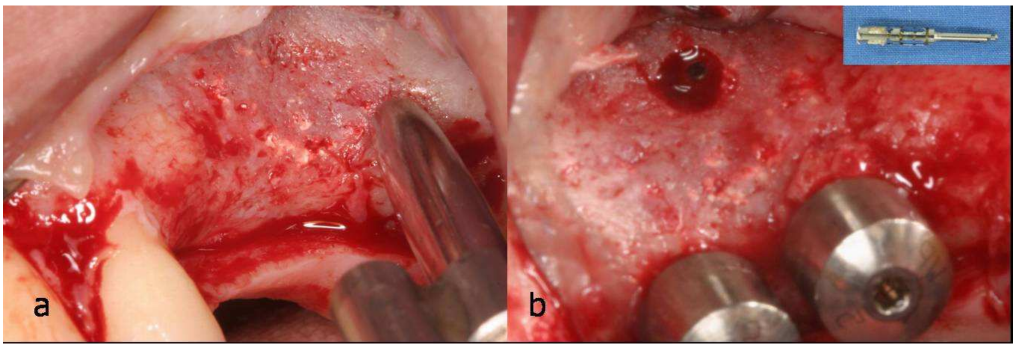

Figure 2

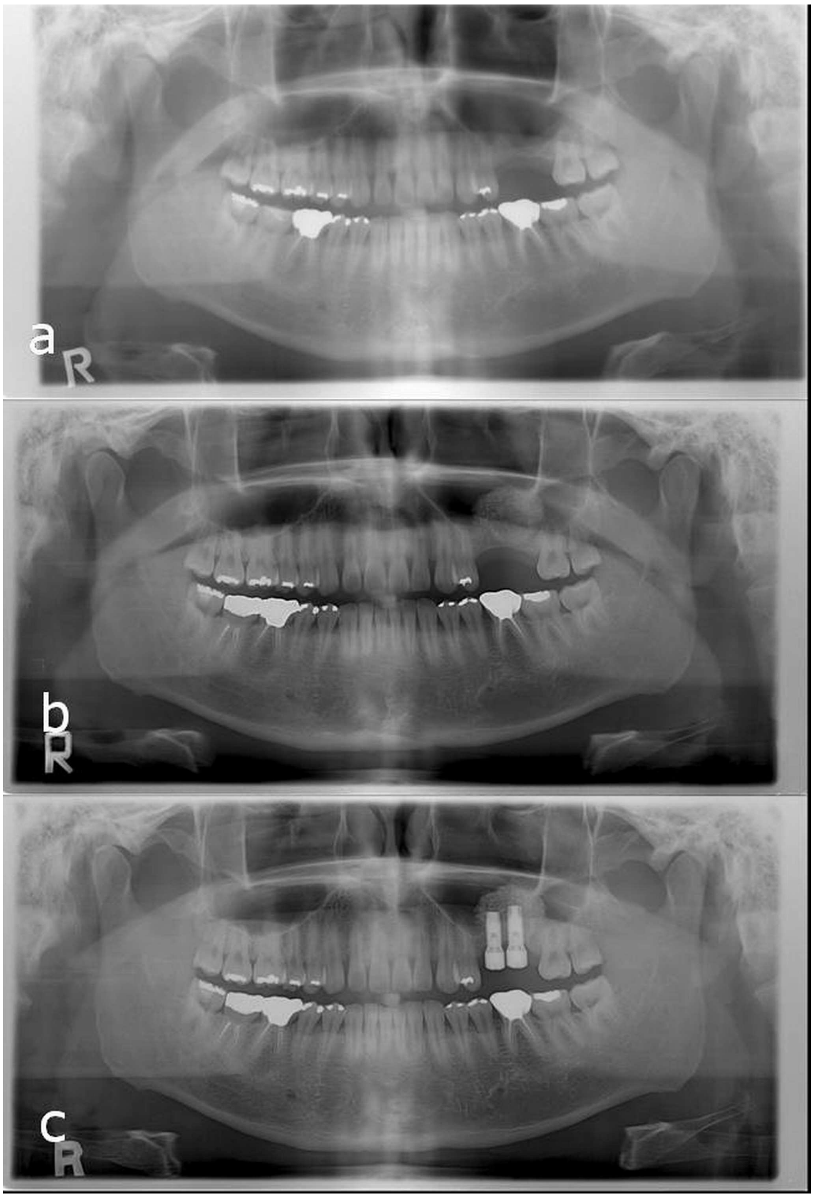

Figure 3

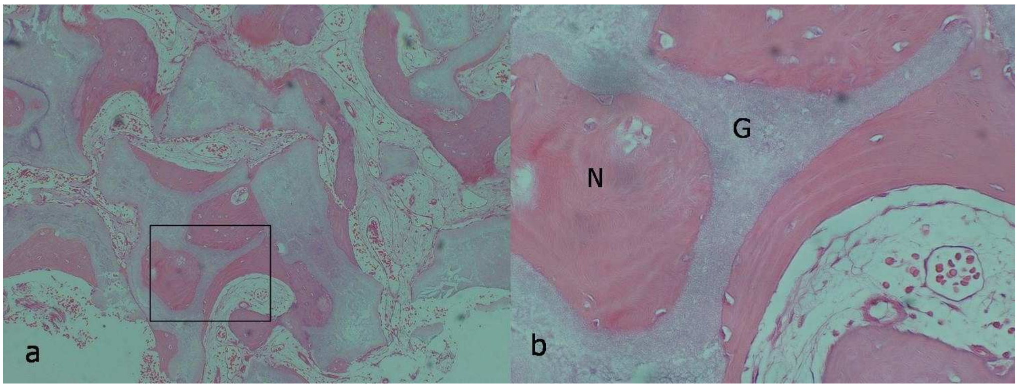

Figure 4

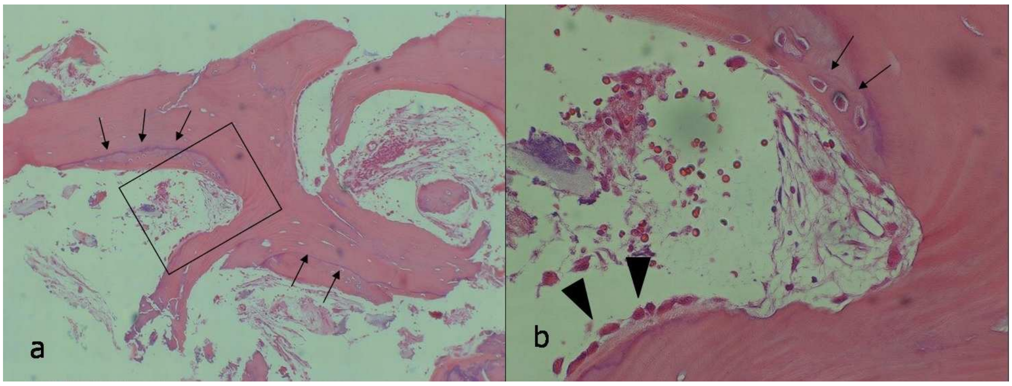

Figure 5

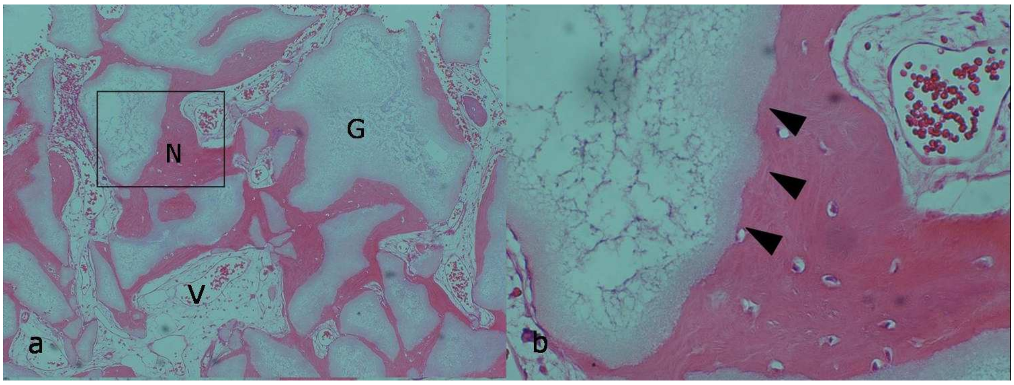

Figure 6

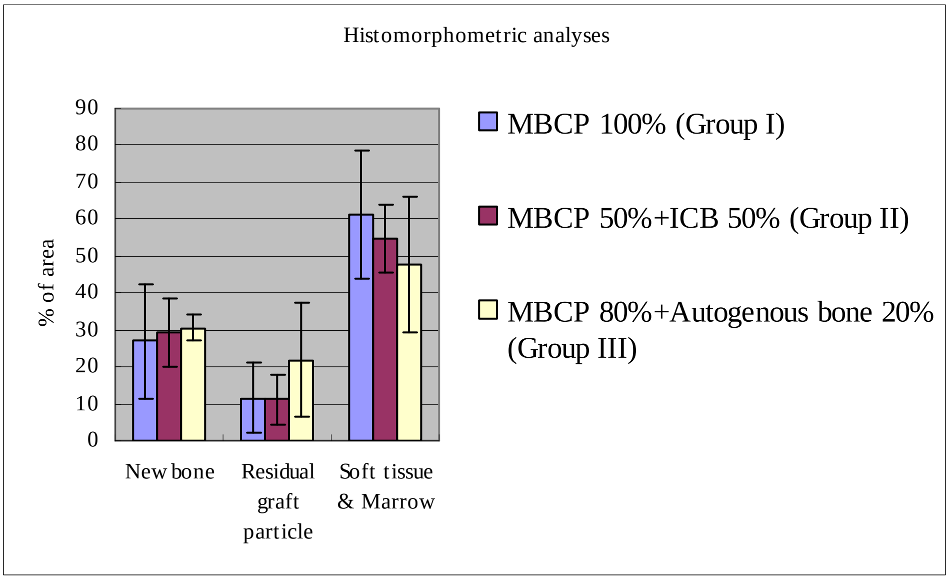

Figure 7

국문요약

합성골 이식재인 Macroporous biphasic calcium phophate를 이용한 사람의 상악동 거상술-임상적, 조직학적 연구

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이 지 현

이제까지 자가골을 비롯하여 많은 종류의 골이식재가 상악동 거상술에 사용되어왔다. Macroporous biphasic calcium phosphate (MBCP)는 hydroxyapatite (HA) 60%와 β-tricalcium phosphate (β-TCP) 40%로 구성된 재료로서, HA가 신생골이 자랄 수 있는 훌륭한 골격을 제공하면서도 β-TCP가 가진 골재생에 대한 활성화 성질 때문에 최적의 골재생을 기대할 수 있다. 이 연구의 목적은 MBCP를 이용한 사람의 상악동 거상술을 임상적, 조직학적으로 평가하는 것이다.

MBCP는 상악동 거상술에서 주재료로 사용되었다. 의학적, 치과적 검사 후 35명의 환자가 선택되었고 이들은 세 그룹으로 나뉘어졌다.

MBCP만을 사용한 그룹, MBCP와 Irradiated cancellous bone and marrow (ICB)를 혼합하여 사용한 그룹, MBCP와 자가골을 혼합하여 사용한 그룹으로 나누어졌으며 상악동 거상술 후 평균 6.83개월 경과한 뒤 조직학적 평가를 위해 골조직생검이 이루어졌으며 이와 동시에 임플란트를 식립하였다.

생검을 통해 얻어진 골조직에서 잔존하는 MBCP 입자 주위로 신생골이 형성된 것을 관찰할 수 있었으며, 조직시편마다 차이는 있었으나 약 30%의 신생골이 생성된 것으로 계측되었다. 또한 상악동 거상술 후 35명의 환자에 총 80개의 임플란트가 식립되었으며 이 중 단 한 개의 임플란트가 보철 전 치유과정에서 탈락되었다. 상악동 거상술 후 약 15개월의 재소환기간 동안 식립된 임플란트는 양호한 임상적 결과를 나타내었다.

이러한 결과를 통해 MBCP는 자가골을 비롯한 골유도능이 있는 것으로 알려진 다른 골이식재와 혼합되지 않더라도 상악동 거상술에서 예측가능한 결과를 낼 수 있는 재료라고 생각할 수 있다.

핵심되는 말 : 치과 임플란트 ; 상악동 거상술 ; 골재생 ; 비교연구 ;
다공성 이상(二相) 인산화 칼슘