A Randomized Controlled Clinical Trial of Alveolar Ridge Augmentation Using rhBMP 2/Hydroxyapatite : Comparative Study on Volume Change With Bovine-derived Xenograft

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Directed by Professor Hyung Jun Kim, D.D.S., Ph.D.

The Doctoral Dissertation
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This certifies that the Doctoral Dissertation of Semjidmaa Khureltogtokh is approved.

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Kh.Semjidmaa

TABLE OF CONTENTS

LIST OF FIGURES

Abstract

A Randomized Controlled Clinical Trial of Alveolar Ridge Augmentation Using rhBMP 2/Hydroxyapatite : Comparative Study on Volume Change With Bovine-derived Xenograft

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Purpose : The aim of this randomized controlled clinical study was to evaluate the early efficacy of recombinant human bone morphogenetic protein 2 (rhBMP-2) with hydroxyapatite granules (BMP-2/HA) as compared with an inorganic bovine bone xenograft (BDX) on ridge augmentation of alveolar bone.

Materials and methods : A total of 20 cases in 17 patients were included in this study. The sites were divided into two groups, each with 10 cases, using a random-number table, and BMP-2/HA and BDX were applied accordingly. Computed tomography (CT) and plain panoramic radiography were obtained immediately and at 4 months after the surgery. CT images

were reconstructed three-dimensionally to measure volumetric changes and linear measurement was executed on panoramic image.

Results : The mean absorption rate of BMP-2/HA and BDX was 13.2 ± 8.8% and 13.8 ± 20.5%, respectively. There was no significant difference between the two materials in the mean value ($P>0.05$). However, the variance of the values in the BDX group was greater than that in BMP-2/HA group. There was no clinically significant complication in both groups.

Conclusions : Both bone substitutes, BMP-2/HA and BDX, were effective in alveolar ridge augmentation to some extent, and BMP-2/HA seemed to be more useful in the complicated bone defect. However, due to the limitations of this study, a long-term follow-up study with dental implantation is required.

Keywords : Bone morphogenetic protein 2, Hydroxyapatite, Bovine-derived xenograft, Alveolar ridge augmentation, Clinical trial, Comparative study

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I. INTRODUCTION

Alveolar bone loss as a result of tooth loss, infection, trauma, or tumor ablation surgery requires reconstruction of bone defects for dental implants. Adequate surrounding bone of implants is essential for successful dental implantation, and various techniques have been developed and used for alveolar bone regeneration[1]. Through the years, different techniques have been used to allow dental implant placement in sites with deficient alveolar bone volume. The guided bone regeneration (GBR) is one of the most popular procedures in out-patient based dental hospital and has also been further advanced with development of new bone substitutes. The autogenous bone graft has been known to have the best prognosis among various bone graft materials and is still considered the gold standard for the majority of applications due to its superior ability to promote osteogenesis

unlike other bone graft materials[2-5]. In spite of this advantage, the autogenous bone graft has some limitations, such as the requirement of additional operation of donor site, increased risk of complications, and limitation in supply amount[5-9]. For this reason, other substitutes including various kinds of allogenic, xenogenic, and alloplastic bone graft materials have been used alone or mixed together for GBR in dental clinics. Unlike these conventional bone substitutes having just osteoconductive capacity or a little osteoinductive capacity, some growth factors, which have proved to have a powerful osteoinductive capacity, such as the bone morphogenetic proteins (BMPs) have been investigated as new graft materials for bone regeneration, and clinically in the oral and maxillofacial area, the application of recombinant human BMP-2 (rhBMP-2) for the sinus augmentation and the localized alveolar ridge augmentation was approved by the Food and Drug Administration (FDA) in 2007[5-7,10,11]. BMPs, the subfamily of transforming growth factor-ß superfamily, are one of the most capable cytokines presenting in the tissues and organs, and plays an important role in development and regeneration of bone acting as a powerful inducer to differentiate mesenchymal progenitor cells into osteoblasts[12-16]. Hence, researchers started to produce it laboratorially through the cloning and replication of its genetic code, consequently obtaining a cell bank at the desired amount and concentration.[17] The cloned protein was named Recombinant Human Bone Morphogenic Protein type 2 (rhBMP-2), and its osteoinductive capability promotes de novo bone

growth at its pure state and high doses.[18,19] Although more than 20 BMPs have been discovered, only BMP-2, -4, -6,-7 and -9 have proved to be capable of driving multipotent cells into an osteoblastic phenotype culture, studies of animals have validated the efficiacy and the safety of rhBMP-2 and rhBMP-7 for bone repair.[20-26] In the past, it was difficult to use clinically the rhBMP, most of which was produced in the mammalian cells such as Chinese Hamster Ovary (CHO) cells, for reconstruction of bone defects because of low productivity and high cost.[27,28] However, mass-production of rhBMP with a low price was made possible with making the rhBMP using prokaryotic expression system such as Escherichia coli, so clinical use of rhBMP has now been widespread.[27,28] There were already many clinical studies using rhBMP-2, however, most of them were case reports, and just a few controlled clinical trials were reported[16,29,30].

The aim of this randomized controlled clinical trial (RCT) was to evaluate the early efficacy of low-dose E. coli–derived rhBMP-2 delivered with HA granules (BMP-2/HA) as compared with an inorganic bovine bone xenograft (BDX), which was the most popular bone graft material in dentistry, on ridge augmentation of alveolar bone.

II. MATERIALS AND METHODS

This study was designed as a single-blinded, randomized, and controlled clinical trial performed at a single center, Department of oral and maxillofacial surgery in the Yonsei University Dental Hospital. The protocols used in this study were approved by the Institutional Review Board for Clinical Research at Yonsei University Dental Hospital (approval no. 2-2015-0001) and observed the Helsinki Declaration and the Good Clinical Practice guidelines. Written informed consents were obtained from all of the enrolled patients to take part in the clinical experiments.

Graft Materials

Bone morphogenetic protein 2 with hydroxyapatite granules (BMP-2/HA ; Novosis-Dent, CG Bio Inc., Gyeonggi-do, Korea) was used for the experimental group. It was composed of hydroxyapatite granules (0.5g ; granule size, 0.6 to 1.0 mm ; pore size, 200 to 250 μm), lyophilized *Escherichia coli*-derived recombinant human BMP-2 (ErhBMP-2 ; 0.5mg), and distilled water (0.5mL). After ErhBMP-2 was dissolved in sterilized distilled water, the solution was gently mixed with hydroxyapatite granules for more than 10 minutes so that it would be evenly distributed into the pores. Bovine-derived xenograft (BDX ; Bio-Oss, Geistlich Pharma AG, Wohlhausen, Switzerland ; 0.5g per bottle ; small granules, 0.25 to 1.0 mm) was used for the control group. The amount of used graft materials was determined by the defect size of each individual subject.

Sample size and subjects

The number of subjects was 10 in the control and experimental group, respectively. The patients had a median age of 61 (range 20-81) years and were in good general health. There were a few published controlled clinical trials of ridge augmentation with BMP-2 yet, so this study was designed as a therapeutic exploratory clinical trial to evaluate the efficacy and safety of BMP-2/HA on ridge augmentation of alveolar bone, comparing with BDX. Therefore, the number of subjects was decided for clinical and radiologic outcome based on clinical experiences of operator and previous research. The inclusion criteria of subjects are as follows : The patients who had lack of alveolar bone vertically or horizontally for dental implantation; who were more than 18 years old having complete growth of jaw bone; who were deemed possible to take part in this clinical trial by the researchers; and who provided written informed consent to participate in this clinical experiment. On the other hand, the followings were excluded : Candidates who had systemic diseases such as autoimmune disease that affect bone turnover, bleeding disorders and uncontrolled diabetes mellitus; who had mental illness or suspected status; who had past history of allergic reaction to hydroxyapatite or rhBMP-2; who were pregnant women or nursing mothers; who were having malignant tumors or getting chemotherapy; who were alcoholics; and who were deemed inapposite to participate in this clinical trial by the researchers.

Randomization

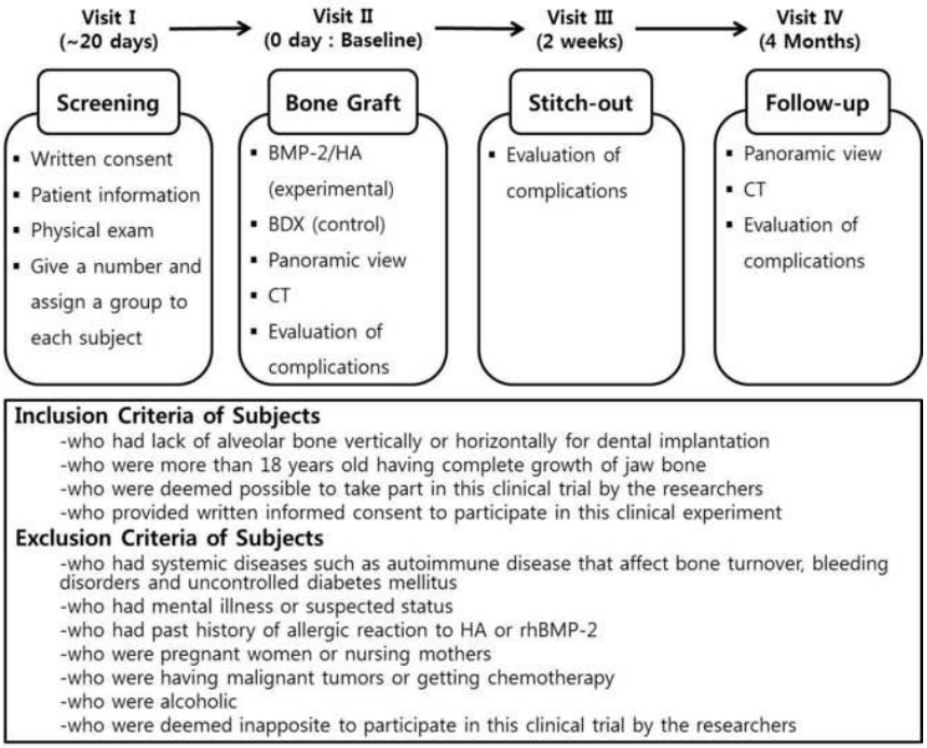
Random group assignment was performed using block randomization by a statistician. Computer-generated random numbers were given to the subjects, and the surgeon received the assigned materials on operation day. The enrolled individuals were not informed of the materials, to be used to in this research.

Timetable and surgical procedures

This clinical study was conducted in four sequences (4 visits per subject), and the detailed was summarized in Figure 1. A single surgeon did all operations for bone augmentation and all operations were performed under local anesthesia. The surgical technique used in this study was different from a conventional one for guided bone regeneration, using crestal, vertical, and releasing incisions, and occlusive barrier membranes. Instead, an enveloping method which was composed of a vestibular incision and elevation of the periosteum spacing for bone graft materials was used. This technique can prevent graft materials spreading around, and decrease risk of complications, such as wound dehiscence. After forming the envelopes, the operator made several holes with fissure bur for decortication on recipient sites and filled graft materials into the envelopes. Membranes covering graft materials were not used, and just the periosteum was kept intact. Horizontal mattress suture was carried out with 4-0 Vicryl®(Polyglactin 910, Ethicon, United States), and then the stitches were removed after 2 weeks

(Figure 2). Antibiotics (100mg Cefcapene pivoxil), analgesics (368.9mg IbuprofenArginine) and antacids (31.5mg Ranitidine HCl) were prescribed for premedication (taking 1 tablet of each, 1 hour before surgery) and post-operative medication for 5 days.

Figure 1. Flow diagram of a comparative RCT of rhBMP-2/HA and BDX for alveolar ridge augmentation, and the inclusion and exclusion criteria subjects



Radiographic analysis

Two radiographic modalities including panoramic view and CT at immediate (IMPO) and 4 months after operation (POD4M) were used for

evaluation of effectiveness of bone augmentation. The primary endpoint was volume change of grafted bone substitutes, and it was calculated using three-dimensional (3D) reconstruction software(OnDemand3D, Cybermed Inc., Seoul, Korea). All CT images were processed into DICOM format, and reconstructed three-dimensionally using the software. The setting value of threshold of density for detection of grafted bone was determined by pairing between the volume of actual used grafted bone and calculated volume on 3D reconstruction software, and was set at 400~1000 HU. Then, each patients' reconstructed CT images of IMPO and POD4M were overlapped each other in three axes, coronal, sagittal and axial. The amount of volume change was measured automatically by subtracting POD4M reconstructed CT image (3D-image) from IMPO 3D-image in the software (Figure 2). The secondary endpoint was the approximate amount of vertical bone gain on defect sites, measured on POD4M panoramic radiograph (Figure3). Additionally, degree of cross-sectional concavity (defect type) of the recipient sites also could affect the result of bone graft, so the defects were classified into 3 types depending on cross-sectional concavity of the middle of defects appeared on CT images (Figure 4).

Figure 2. Fused image of both post-op CT images of each subject by overlapping each other in 3 sectional aspects. Blue dotted line indicates a maintained grafted material at POD4M, and white dotted line indicates a portion of absorption, resulted by subtraction POD4M images from IMPO images.

3D-image of the absorbed portions of the grafted materials (indicated by white arrows) is seen on the right side. The volume of maintained grafted material and portion of absorption was automatically calculated using the image software

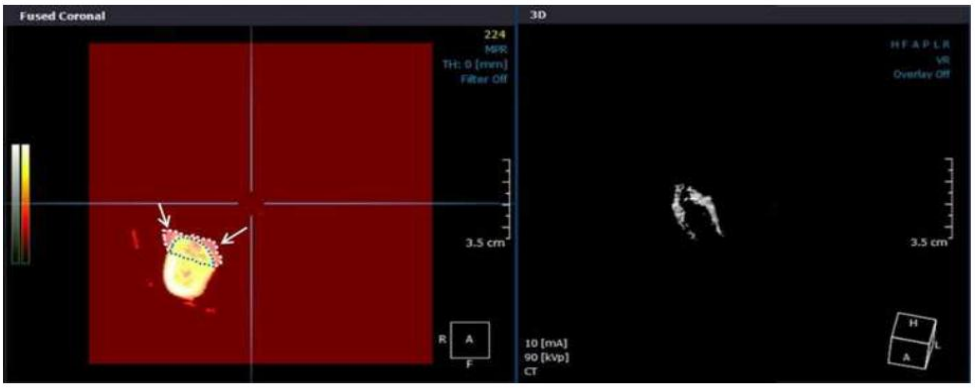


Figure 3. Preoperative, IMPO, and POD4M panoramic radiograph. The approximate amount of vertical bone augmentation (d) was measured on POD4M panoramic radiograph

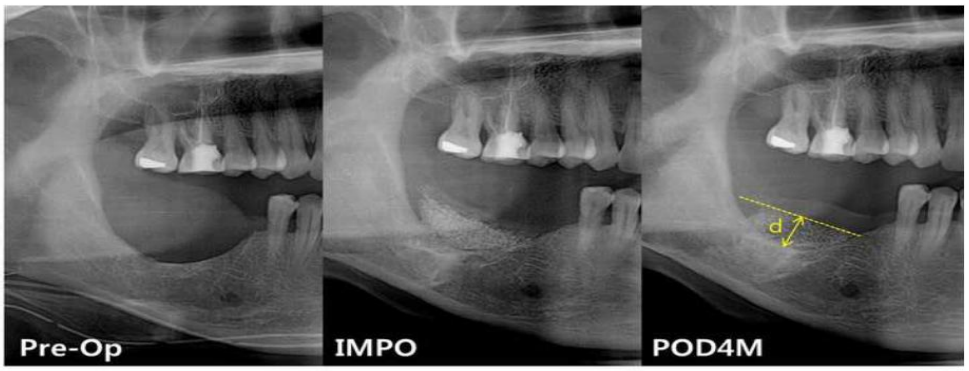
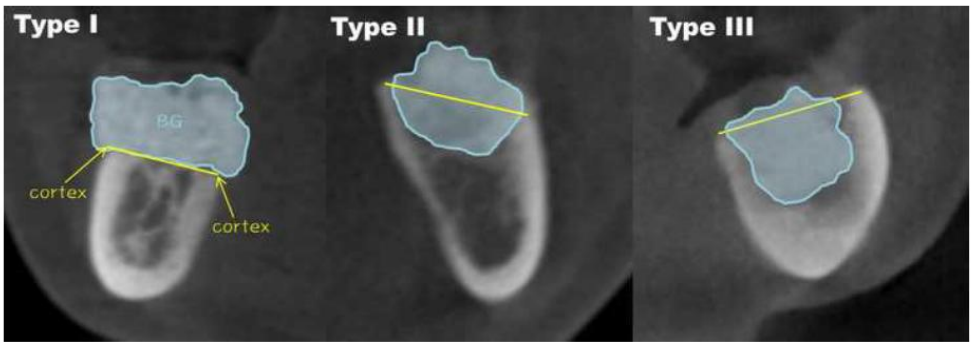


Figure 4. The degree of cross-sectional concavity (Defect Type) of the recipient sites also could affect the result of the bone graft, so the defects were also classified into 3 types depending on immediate post-op CT images. In Type I, most of the bone graft materials (BG) were located above the

linear line connecting the most superior points of buccal and lingual cortices of the jaws. In Type II, the line went through the middle portion of BG, and in Type III, most of BG were located below the line



Statistical analysis

Statistical analysis was performed using PASW statistics 18 software (IBM SPSS Inc., Chicago, IL). The primary outcome of interest was bone growth as measured proxy variables, including percentage of the change in alveolar ridge width or percentage of new bone formation. The mean and standard deviation of all parameters were calculated for both groups in the radiographic analysis. Standardized mean effect was calculated by comparing increases in bone formation between intervention and control groups. The Shapiro-Wilk test was used to determine the normality of data, and primary measured points, volume change and absorption rate, were decided as nonparametric variables except absorption rate of BMP-2/HA group. On the other hand, the other variables, the approximate amount of vertical bone gain, showed a normal distribution. Therefore, the significance of any differences between the two groups was approved by

Mann-Whitney U-test for nonparametric data and independent t-test for parametric data ($p = 0.05$).

III. RESULTS

Subjects

18 volunteers consented to participate in this clinical experiment, and all participants satisfied the screening criteria. One patient postponed the operation due to personal reason and was dropped out. The final eligible consenting 17 patients, for a total of 20 cases (one patient had 3 defect sites, the other patient had 2 defect sites), were enrolled in this clinical study. 20 defect sites were randomly divided into two groups : experimental group (n=10) and control group (n=10). Subjects in the experimental group were 54.8 ± 13.18 years old, and the ratio between male and female was 8 : 2. In the control group, subjects were 60.4 ± 11.36 years old, and the ratio between male and female was 7 : 3. The enrolled bone defects were caused by various causes, such as chronic periodontitis, ablation of benign and malignant tumors, osteomyelitis, removal of implants, and extraction of hopeless teeth. Among them, chronic periodontitis (10 cases) was the most common cause of bone defects. According to plan, post-operative follow-ups were performed at 2 weeks and 4 months after bone grafts, and this clinical experiment was completed at 4 months ± 2 weeks after operation in all participants. There was no dropout during the experimental period.

Efficacy

The width of the alveolar ridge was recorded at a baseline and at 4 months to evaluate the horizontal bone gain. The absorption rate of BMP-2/HA and BDX were 13.2 ± 8.8% and 13.8 ± 20.5%, respectively. There was no significant difference of absorption rates between the two groups (p=0.287). And the range of the absorption rate was 4~29% in the experimental group and 0~56% in the control group. The approximate amount of vertical augmentation of POD 4M were 7.12 ± 3.28 mm in the BMP-2/HA group and 7.31 ± 4.43 mm in the BDX group with no significant difference between the two groups as well (p=0.064). Therefore, the BMP-2/HA was non-inferior to the BDX for ridge augmentation of alveolar bone defects, and both materials seem to be useful for it, though the measurement of vertical bone gain was not precise. There was also no significant difference of the amount used and the amount of volume change between the experimental and the control groups (p=0.163, 0.199, respectively)(Table 1).

Table 1

Comparison of results between the experimental and the control groups: data are mean (SD). Statistical analysis = Mann-Whitney U test, and independent t test ($p = 0.05$).

Variable	Experimental	Control	p value
Amount used (ml)	0.75 (0.49)	0.60 (0.45)	0.163
Change of volume (ml)	0.105 (0.099)	0.107 (0.205)	0.199
Absorption rate (%)	13.2 (8.8)	13.8 (20.5)	0.287
Vertical augmentation (mm)	7.12 (3.28)	7.31 (4.43)	0.064

Safety

Mild complications including inflammation, swelling and wound dehiscence, which did not affect the result, occurred in 5 cases, and there were no dropout due to them. Just one patient, who had mild inflammation with small gumboil formation, received a prescription for antibiotics and anti-inflammatory drugs, and the problem was solved in a week. The other 4 patients with mild complications were instructed to care for the wounds with saline mouthwash, and they recovered quickly. The complications are summarized in Table 2.

Table 2.

	Case	Age/ Gender	Sites	Amount Used (cc)	[1]Change of Volume (cc)	Absorption Rate (%)	Defect Type	[†]Ver. Aug. (mm)	Complications
Experimental	1	64/M	#26,27	0.5	0.037	7%	1	4.22	None
	2	55/M	#37	0.5	0.022	4%	1	5.33	Mild inflammation with small gumboil formation
	3	57/M	#26,27	1	0.126	13%	1	11.25	None
	4	20/M	#44,45,46,47	1	0.295	29%	1	10.91	None
	5	51/M	#37	0.5	0.119	24%	2	3.16	Mild to moderate swelling
	6	61/F	#34	0.5	0.056	11%	1	2.25	None
	7	52/F	#45,46,47	2	0.262	13%	1	10.08	Wound dehiscence with slight inflammation
	8	66/M	#47	0.5	0.029	6%	1	6.62	None
	9	61/M	#16,17	0.4	0.082	21%	1	8.42	None
	10	61/M	#46,47	0.6	0.022	4%	2	8.97	None
Control	11	62/F	#27	0.5	0.063	13%	2	3.48	None
	12	44/F	#46,47	1.2	0.675	56%	1	4.27	Slight wound dehiscence
	13	81/M	#36,37	1.5	0.116	8%	3	14.11	None
	14	68/F	#46	0.5	0.001	0%	3	10.51	None
	15	46/M	#45	0.25	0.117	47%	2	3.18	Slight wound dehiscence
	16	51/M	#37,38	0.9	0.083	9%	1	2.47	None
	17	66/M	#16	0.25	0.000	0%	2	7.51	None
	18	66/M	#26	0.25	0.000	0%	2	10.4	None
	19	65/M	#26	0.3	0.014	5%	3	13.21	None
	20	55/M	#26	0.3	0.000	0%	2	3.94	None

[1]Change of Volume = Volume of (Immediate post-op 3D-reconstructed image – POD 4M 3D-reconstructed image)

[†]The approximate amount of vertical bone gain was measured on panoramic radiography of POD 4M, so it cannot be a precise value.

IV. DISCUSSION

The present study investigated the early efficacy of BMP-2/HA focusing on volumetric change for the ridge augmentation of alveolar bone defect using 3D analysis compared with that of BDX. In previous studies of BMPs, there were a few RCTs for evaluation of maxillary sinus floor augmentation[29-31] and less RCTs for alveolar ridge augmentation[5,29]. Although BMP has been well known as an excellent growth factor having a powerful osteoinduction capacity in many animal studies[27,32,33], there are many controversies for its efficacy in human subjects. In the latest systematic review, analysing 8 RCTs which were published from 1980 to January 2014, the researchers concluded that rhBMP-2 substantially increased bone height for localized alveolar ridge augmentation, however, autograft or allograft in maxillary sinus floor augmentation[29]. Thus, rhBMP-2 is increasingly becoming a feasible alternative to autograft, avoiding the need for a second surgical intervention and the consequent morbidity and pain resulting from bone harvest, as well as the loss in graft quality and height.[34] Another systematic review for 7 publications regarding alveolar ridge and maxillary sinus augmentation using rhBMP-2 with an absorbable collagen sponge (ACS) as a carrier concluded that rhBMP-2/ACS appeared to be a promising alternative to autogenous bone grafts for alveolar ridge/maxillary sinus augmentation, though bone formation following autogenous bone graft was significantly greater than rhBMP-

2/ACS for maxillary sinus augmentation[16]. Collectively, these reports suggested that rhBMP-2/ACS seems to be a safe and effective alternative to bone grafts in patients who require bone augmentation procedures, which allows long-term functional loading of endosseous oral implants. Clinical studies of BMP showing different results may be attributed to the fact that efficacy of BMP depends on its delivery system which functions for releasing control of growth factors and space maintaining for new bone formation.

The primary role of the BMP delivery system is to maintain a growth factor in bone defect site according to anatomical size, position, and vascularity of the defect site for regeneration and recovery of bone during regeneration period, and so it should allow the regenerative tissue forming cells to migrate to the tissue defect site, and to proliferate and differentiate[12-14]. Two requirements are essential for these BMP carriers, 'localized' and 'release-controlled' delivery[12,13], and additionally essential factors such as safety, efficiency, convenience, and economics should be satisfied for the clinical application of BMP. Thus, many types of delivery materials have been studied and published. Collagen sponges performed well as carrier materials,[35,36] although, different studies using rhBMP-2 in an ACS for alveolar ridge augmentation reported a limited bone regeneration[37-39] due to the failure of the ACS to adequately support support the supraalveolar wound space. In this clinical trial, HA, categorized into inorganic materials,

was used as a BMP carrier. It is similar to the bone structure and has benefits of osteoconductive capacity and affinity for BMPs, but it also has demerits of fragility and difficulty of manipulation[13,14].

As far as we are concerned, this was the first clinical trial of BMP-2 using HA as a carrier for alveolar ridge augmentation. The BMP-2/HA group had similar particle and pore size and similar material architecture to BDX, and it was the most popular bone graft material in dentistry worldwide, so it was used as the control group[30]. For the analysis, it was premised that the bone substitutes would be absorbed in the early healing phase after grafting and the position of grafted materials would not change, though rigid barriers such as a titanium mesh were not applied in this study. When we calculated the amount of volume changes of the grafted materials during the experimental period, it was measured by subtraction POD 4M 3D images from immediate post-op 3D images and because all values measured reversely by subtraction immediate post-op 3D images from POD 4M 3D images, were zero. Besides the surgical technique, which consisted of vestibular incision and making an envelope preserving a periosteum intact, helped bone graft materials to be maintained in their position. Although the function as a barrier of the periosteum was controversial, some articles reported that an intact periosteum could act as a barrier membrane against ingrowth of soft tissue and promotes osteogenesis[40-43]. Therefore, any artificial membranes were not used in this study. Following this study, the

absorption rates of both materials were not significantly different from each other, however the range of absorption rate of BDX was wider than that of BMP-2/HA though the defect types of recipient sites of the control group seemed to be more favorable than that of the experimental group by coincidence. The approximate amounts of vertical augmentation on panorama radiograph at POD 4M were similar between both groups with no significant difference was found. Of course, there was a limitation to the measurement on the panoramic radiograph due to its difficulty of standardization. Nevertheless, it seemed that bone grafts with both materials were effective in ridge augmentation for alveolar bone defects. Additionally, we attempted to verify other correlation between the variables with various statistical methods. However, there was no specific relationship between them.

Adverse events regarding rhBMP-2 were reported, including oral edema, prolonged swelling, mouth pain, oral erythema, and especially, extensive swelling, seroma formation, cystic bone lesion, and cancer development from high dose of rhBMP-2[5,29,30]. Special note was made on studies demonstrating that BMP-2 can induce angiogenesis in developing tumors [44,45], thus showing increased pathogenicity of oral cancer cell lines after transient exposure to rhBMP-2. However, there were no major adverse events and just minor complications reported in dental patients exposed to rhBMP-2[11,29]. This clinical trial also showed 3 minor complications in the

experimental group, including inflammation, swelling and wound dehiscence, and most of them were resolved in 1~2 weeks spontaneously. Generally, soft tissue dehiscence is one of the most frequent complications after GBR procedure[46], but BMP is known to have the ability to promote soft tissue healing[47], so it can be helpful in wound coverage.

This clinical trial showed that both bone substitutes, BMP-2/HA and BDX, were effective in alveolar ridge augmentation to some extent and BMP-2/HA was seemed to be more useful in the complicated bone defect. However, this study was carried out during short-term and lacked a histomorphometric analysis, so a long-term follow-up with dental implantation and additional research should be necessary.

V. CONCLUSION

Both bone substitutes, BMP-2/HA and BDX, represent a valuable treatment option for ridge augmentation enhancing the maturation process of bone regeneration. Although BMP-2/HA seemed to be more useful in the complicated bone defect. However, due to the limitations of this study, a long-term follow-up study with dental implantation is required to yield predictable and relible bone regeneration.

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Abstract (Korean)

치조골 증대술에서 NOVOSIS®-Dent 와 Bio-Oss 와의 골 치유 양상 비교

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연구 목적: 이 무작위 비교임상연구의 목적은 치조골 증대술에서 hydroxyapatite 입자를 운반체로 하는 bone morphogenetic protein-2 (BMP-2/hydroxyapatite)를 사용하였을 때, inorganic bovine-derived xenograft (BDX)과 비교하여 초기 체적 변화를 평가하기 위함이다.

실험 재료 및 방법: 20 개의 골결손 부위가 무작위 배정을 통해 BMP-2/hydroxyapatite 와 BDX 두 군으로 배정되었다. 수술 직후와 술 후 4 개월째에 컴퓨터단층촬영과 치과파노라마방사선사진이 촬영되었으며, 체적 변화의 측정을 위해 컴퓨터단층촬영 영상은 삼차원적으로 재구성되고 치과파노라마방사선사진 상에서 이차원적인 계측이 시행되었다.

연구 결과: BMP-2/hydroxyapatite와 BDX 군의 흡수율은 각각 13.2±8.8%와 13.8±20.5% (mean±standard deviation)였다. 평균값은 두 군 사이에서 유의미하게 다르지 않았으나 (p>0.05), BDX 군이 BMP-2/hydroxyapatite 군보다 높은 표준편차를 갖는 것이 관찰되었다. 모든 군에서 임상적으로 특기할만한 합병증은 발생하지 않았다.

결론: BMP-2/hydroxyapatite 와 BDX 모두 치조골 증대술에 효과적이며, 좀 더 난해한 골 결손부에서는 BMP-2/hydroxyapatite 가 좀 더 유용할 것으로 보인다.

핵심단어: 골형성 단백질; 하이드록시아파타이트; 소뼈유래
이종골이식; 치조골 증대술; 체적 변화; 임상시험