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Void space and long-term volumetric changes of maxillary sinus floor augmentation with comparison between hydroxyapatite soaked with bone morphogenetic protein 2 and anorganic bovine xenograft alone

Hoon Joo Yang [a, b], Soon Jung Hwang [c, *]

[a] Orthognathic Surgery Center, Seoul National University Dental Hospital, 101, Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea
[b] Department of Oral and Maxillofacial Surgery, School of Dentistry, Seoul National University, 101, Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea
[c] Hwang Soon Jung's Dental Clinic for Oral and Maxillofacial Surgery, Woonam Building, 2,3 F, 349, Gangnam-daero, Seocho-gu, Seoul, 06626, Republic of Korea

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ABSTRACT

Purpose: We hypothesized that the void volume after maxillary sinus floor augmentation (MSFA) with recombinant human bone morphogenetic protein-2 (rhBMP-2) would be larger than that without rhBMP-2, and filled with bone in the long term. The aim of this study was to analyze the occurrence of void space and long-term volumetric changes after MSFA with rhBMP-2 and hydroxyapatite (BMP-2/H).
Material and methods: In 25 subjects, MSFA was performed with BMP-2/H (group I) or an anorganic bovine xenograft (group II). Computed tomography scans were taken twice, at 3 months (T1) and at least 24 months (T2) after surgery. Total volume (TV), bone volume (BV), and void volume (VV) were measured and analysed statistically.
Results: While similar amounts of graft material were used, the TV was significantly larger in group I than in group II ($p = 0.014$). The VV showed a tendency to be larger in group I than in group II. VV reduction up to T2 was significantly greater in group I than in group II. Consequently, the BV at T2 was significantly greater in group I than in group II by 36% ($p = 0.014$).
Conclusion: This study showed that our hypothesis was valid. rhBMP-2 is effective for long-term bone regeneration after MSFA.

1. Introduction

Maxillary sinus floor augmentation (MSFA) is the most commonly performed graft procedure for treating alveolar height deficiency prior to implant placement in the posterior maxilla (Boyne et al., 2005; Triplett et al., 2009; Peng et al., 2013). Various bone grafting materials are used for MSFA, with the amount of bone graft material used depending on the vertical and horizontal extension of sinus elevation during surgery. It has also been reported that recombinant human bone morphogenetic protein 2 (rhBMP-2), the most powerful osteoinductive growth factor, can be successfully used for MSFA (Boyne et al., 2005; Triplett et al., 2009; Kao et al., 2012; Kim HJ et al., 2015; Kim MS et al., 2015; Kang et al., 2016).

The most frequent clinical complication after rhBMP-2 application is swelling of the neighboring soft tissue. Swelling has been observed at the surgical site in animal experiments with implants coated with rhBMP-2 (Leknes et al., 2008; Wikesjö et al., 2008). This complication leads to prohibition of its use in the cervical spine due to the risk of serious obstruction of the airway (Food and Drug Administration, 2008). This issue also applies to MSFA. While bone augmentation on osseous defects below the skin or oral mucosa can lead to compressive force from overlying expanded soft tissue being applied to the grafted space, particulated bone graft materials within the maxillary sinus can be dispersed by postoperative swelling following rhBMP-2 application. This is because the maxillary sinus membrane is easily expanded, especially after overelevation of the sinus membrane during sinus lifting procedures. Therefore, a radiolucent void space after MSFA using a

* Corresponding author. Hwang Soon Jung's Dental Clinic for Oral and Maxillofacial Surgery, Woonam Building, 2,3 F, 349, Gangnam-daero, Seocho-gu, Seoul, 06626, Republic of Korea. Fax: +82 2 525 4738.
E-mail addresses: yanghoonjoo@snu.ac.kr (H.J. Yang), soonhwang59@gmail.com (S.J. Hwang).

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particulated graft material can occur more frequently in cases with rhBMP-2 application than in cases without rhBMP-2 use, especially at high concentrations of rhBMP-2 (Leknes et al., 2008; Kang et al., 2016).

These voids can be seen in panoramic radiography (Fig. 1), and their three-dimensional (3D) form and size can be easily confirmed by computed tomography (CT) after MSFA. In animal experiments, unevenly dispersed particles and radiolucent voids were observed in seven of eight rabbits following MSFA using a biphasic calcium phosphate (BCP) carrier soaked with a high concentration of rhBMP-2 (Hong et al., 2016). In a single case report by Kang et al. (2016), the void space after MSFA using rhBMP-2 led to an increased volume of the augmented maxillary sinus 6 months postoperatively. A void space can also occur in MSFA using graft materials without rhBMP-2, because of the difficulty in condensing the graft material, as a result of the limited surgical field and the open-ended posterior region of the space under the elevated maxillary sinus membrane (Tsai et al., 2015).

Although void spaces can be observed in MSFA with or without rhBMP-2, long-term changes in the 3D void volume have not been reported. We hypothesized that the void volume after maxillary sinus floor augmentation (MSFA) with recombinant human bone morphogenetic protein-2 (rhBMP-2) would be larger than that without rhBMP-2 and would fill with bone in the long term. The aim of this study was to analyze the long-term 3D volumetric changes, including the void space, by 3D CT, comparing MSFA using hydroxyapatite (HA) granules soaked with rhBMP-2 with MSFA using anorganic bovine xenografts (ABX) without rhBMP-2.

2. Material and methods

2.1. Patients

This study was a follow-up of a previous prospective, randomized, single-blind, clinical study (Clinicaltrial.gov NCT01634308) (Kim HJ et al., 2015). Among the subjects who received allocated interventions after randomization in a previously reported clinical trial at Seoul National University Dental Hospital ($n = 37$), patients who agreed to participate in a long-term follow-up were included in the present study ($n = 25$). Patients who did not agree to undergo follow-up CT ($n = 10$) or had adverse events ($n = 2$; a cerebral infarct and maxillary sinusitis) were excluded (Fig. 2). The study was conducted as a clinical observation study after the previous clinical trial, and was performed without any sponsorship.

The inclusion criteria for the previous randomized, clinical study were age between 40 and 70 years, and residual alveolar bone size between 2 mm and 6 mm in height and more than 6 mm in width, which was confirmed by reformative CT for dental implants. The exclusion criteria were individuals who had taken medications known to affect bone turnover, such as glucocorticoids, bisphosphonates, or other drugs such as immunosuppressive or antirheumatism medication, and smokers who smoked more than 10 cigarettes per day. Patients with systemic diseases such as uncontrolled diabetes mellitus and primary or secondary hyperparathyroidism, as well as those with local diseases such as uncontrolled periodontitis or maxillary sinus pathology, were also excluded.

This study was conducted with institutional review board approval from the Seoul National University Dental Hospital (CDE10003) and complied with the EQUATOR guidelines (CONSORT). The study procedure was performed in accordance with the Declaration of Helsinki (2008 revision). Before the procedure, a detailed explanation and written informed consent form were provided to all subjects. Only those who agreed to undergo the protocol were included in the study.

After enrollment by a clinical tester, the subjects were not informed about their graft material assignment. Prior to randomization, a registration number was given to each subject by a clinical tester according to the subject enrollment number. The assignment of graft material to each registration number was done by block randomization, which was conducted by a statistician using SAS software (SAS Institute Inc., Cary, NC, USA). Finally, 25 patients who were followed up for at least 2 years with CT scans after MSFA were included and evaluated.

2.2. Surgical procedure and graft materials

Every surgery was performed under local infiltration anesthesia with 2% lidocaine. After raising a mucoperiosteal flap by making an incision on the alveolar crest, combined with a vertical releasing incision, the lateral surface of the maxilla was exposed. A window (10–15 mm in height and 15–20 mm in width) was made on the lateral maxillary wall using a rotary instrument under cooling with physiological saline. The lower border of the window was located 4–5 mm away from the floor of the maxillary sinus in order to create similar conditions for new bone formation and a similar void space to augment with graft materials. The bony window was removed. The sinus membrane was elevated upward to the upper border of the window and *Escherichia coli*-derived rhBMP-2 was delivered with HA granules (Novosis®-Dent; CGBio Inc., Gyeonggi-do, Korea), or particulated ABX (Bio-Oss®; Geistlich Pharma AG, Wohlhausen, Switzerland) was grafted into the elevated space. The wound was carefully closed with resorbable suture materials (Vicryl 4.0; Ethicon Inc., Cincinnati, OH, USA) without the application of a barrier membrane at the window site.

The HA granules soaked with rhBMP-2 (BMP-2/H) were 0.60–1.00 mm in diameter, with pore size ranging between 200 μm and 250 μm. The lyophilized rhBMP-2 (0.5 mg/bottle) was dissolved in distilled water (0.5 ml/bottle), and then gently mixed with HA granules (0.5 g/bottle) so that it would be evenly distributed into the pores. The granule size of the ABX (0.5 g/bottle) was between 0.25 mm and 1.00 mm. The amount of graft material used was determined by the size of the elevated space within the maxillary sinus and the edentulous span of each subject. As a result, 0.5–2.0 g

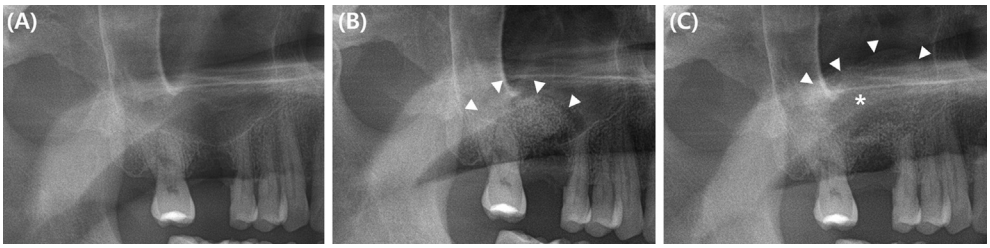

Fig. 1. Void formation after MSFA using rhBMP-2 and HA granules. Orthopantomograms before surgery (A), immediately after surgery (B), and 2 weeks after surgery (C). The arrowheads denote the boundary of the augmented maxillary sinus. An asterisk marks the void formed inside the augmented maxillary sinus.

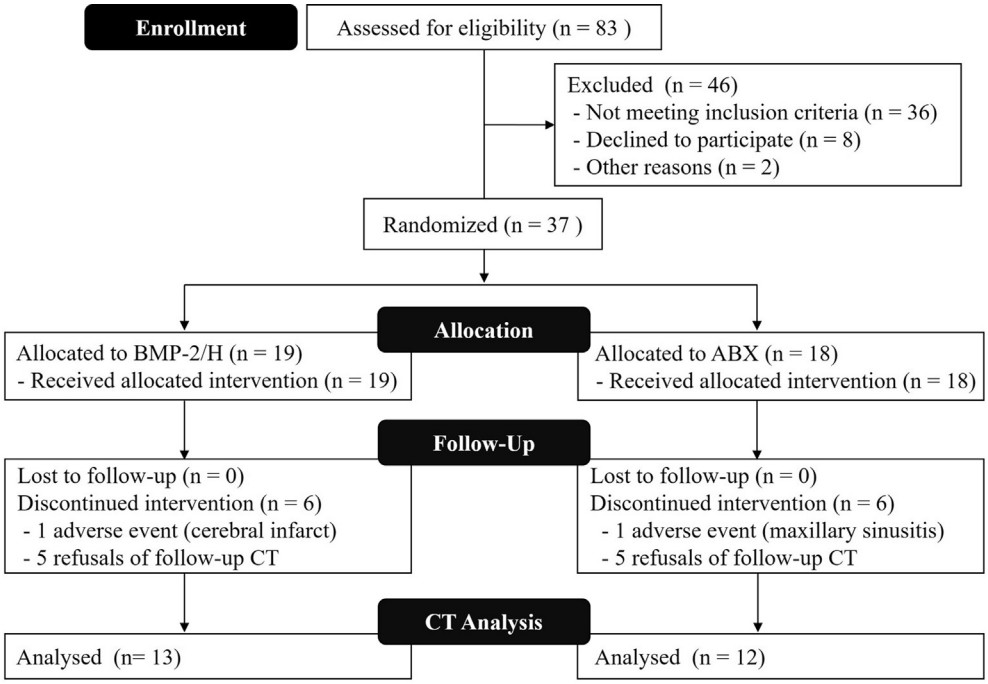

Fig. 2. Flow diagram of a randomized clinical trial of recombinant human bone morphogenetic protein 2 with hydroxyapatite (BMP-2/H) for maxillary sinus floor augmentation compared with anorganic bovine xenograft (ABX).

of graft material was used. Corresponding with the amount of graft material, the total dose of rhBMP-2 was 0.5–2.0 mg.

2.3. CT analysis

After MSFA, conventional multislice CT (SOMATOM Sensation 10; Siemens, Munich, Germany) was conducted at a 3-month follow-up (T1) and at a long-term follow-up point at least 24 months after surgery (T2). Implants were placed immediately after the T1 CT scan, on the same day. The CT images were obtained under 120 kVp and 80 mAs, with a slice thickness of 1.5 mm.

The CT images were analyzed three-dimensionally using Mimics 19.0 (Materialise, Leuven, Belgium) (Fig. 3). Three parameters, total volume (TV), volume of the bone and bone graft material (BV), and volume of the void (VV) were measured. The measurements were conducted independently by two examiners. TV was defined as the area below the elevated sinus mucosa in the maxillary sinus, with a Hounsfield unit (HU) value of −900 or higher. BV was defined as an area with an HU value of 300 or more within the space defined by the TV. Finally, the VV was defined as the area excluding the volume of the bone and bone graft material in the TV. These three parameters were measured on the T1 and T2 CTs in the same manner.

2.4. Statistical analysis

Statistical analyses were performed using IBM SPSS software version 21 (IBM Corp., Armonk, NY, USA). In each group, changes in the three volumetric parameters with time were evaluated by use of the Wilcoxon signed-rank test. The Wilcoxon rank-sum test was used to compare the results of CT analysis between group I and group II. The frequency of VV (%) based on 10% or 20% VV in both

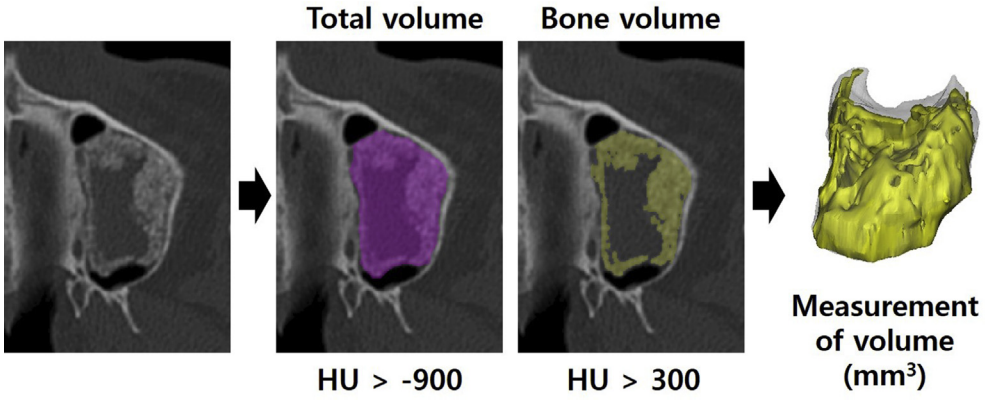

Fig. 3. CT analysis method. In each axial plane of the CT, the total area and the bone area in which the MSFA is defined by HU are established, and volumes are calculated by combining them together. Total volume applies to areas below the elevated sinus mucosa in the maxillary sinus with an HU value of −900 or higher. Bone volume applies to areas with an HU value of 300 or more within the space defined by the total volume.

groups was compared using Fisher's exact test. p-values of less than 0.05 were considered to be statistically significant.

3. Results

A total of 25 subjects were evaluated. Patients were classified into two groups according to the graft materials used for the maxillary sinus augmentation. For group I (n = 13; M:F = 11:2; mean age 54.2 years, range 42–64 years), BMP-2/H was used, while ABX was used in group II (n = 12; M:F = 9:3; mean age 56.2 years, range 44–64 years). The amount of particulate HA used in group I was 1.96 ± 0.14 g, while the amount of rhBMP-2 used was 1.96 ± 0.14 mg. The amount of ABX used in group II was 1.89 ± 0.23 g. There was no significant difference in the amount of bone graft material used between the groups.

3.1. Void space and volumetric changes of MSFA between T1 and T2 in each group

In group I, seven out of 13 subjects showed a VV of more than 20% of TV at T1, and six subjects had less than 20% of VV (Table 1, Fig. 4). The VV was 1151.5 ± 983.1 mm^3 at T1, decreasing to 570.9 ± 503.3 mm^3 at T2, which was statistically significant (p = 0.002). The ratio of VV/TV decreased significantly from 24.6 ± 17.1% at T1 to 12.5 ± 7.9% at T2 (p = 0.001) (Table 2). In group II, only one of 12 subjects showed a VV of more than 20% of TV at T1, and 11 subjects had less than 10% of VV (Table 1, Fig. 4). The VV was 372.3 ± 180.9 mm^3 at T1 decreasing significantly to 263.4 ± 157.3 mm^3 at T2 (p = 0.019). The ratio of VV/TV decreased significantly from 12.7 ± 6.0% at T1 to 9.0 ± 3.9% at T2 (p = 0.028) (Table 2).

Table 1
Comparison of frequencies between group I and II, based on 20% void volume.

p = 0.030	Void volume (%)		Total
	<20%	≥20%	
Group I	6	7	13
	46.2%	53.8%	100.0%
Group II	11	1	12
	91.7%	8.3%	100.0%
Total	17	8	25
	68.0%	32.0%	100.0%

Statistical analyses were conducted using Fisher's exact test. p-values of less than 0.05 were considered to be statistically significant.

At T1, the TV of the MSFA in group I was 4113.5 ± 1276.5 mm^3, the BV was 2962.0 mm^3 ± 667.0 mm^3, and the ratio of BV/TV was 75.4% ± 17.1%. At T2, the TV had decreased somewhat to 4065.9 ± 1288.8 mm^3, while BV had increased significantly to 3495.0 ± 894.5 mm^3 (p = 0.002) and the ratio of BV/TV had increased significantly to 87.5 ± 7.9% (p = 0.001). In group II, TV and BV were maintained without a statistically significant change from T1 (2951.0 ± 734.7 mm^3 and 2578.7 ± 680.6 mm^3, respectively) to T2 (2834.0 ± 782.5 mm^3 and 2570.6 ± 677.5 mm^3, respectively). No significant change was observed in the absolute volume of BV, but the ratio of BV/TV increased significantly from 87.3 ± 6.0% at T1 to 91.0 ± 3.9% at T2 (p = 0.028) (Table 2).

3.2. Comparison of void space and volumetric changes of MSFA between groups I and II

The frequency of VV being more than 20% of the TV was significantly greater in group I than in group II (p = 0.030) (Table 1). Furthermore, the VV decreased from T1 to T2 in both groups (580.6 ± 627.0 mm^3 in group I and 108.9 ± 148.1 mm^3 in group II), and there was a statistically significant difference between the groups in the size of the decrease (p = 0.026) (Table 3). On the other hand, the two groups did not show a significant difference for VV at both T1 and T2 (Table 2).

Even though similar amounts of bone graft were used in groups I and II, the TV of the augmented maxillary sinus was significantly different. At T1, the TV in group I was significantly larger than that in group II by 1162.5 mm^3 (39.4%, p = 0.014) and this tendency was maintained at T2, while the volume difference at T2 between the two groups was 1231.9 mm^3 (43.5%, p = 0.006). In contrast to TV at T1, there was no statistically significant difference in the BV between groups I and II at T1. However, the BV at T2 was significantly greater in group I (3495.0 ± 894.5 mm^3) than in group II (2570.6 ± 677.5 mm^3) (p = 0.014) (Table 2). Additionally, in group I, BV had increased at T2 by 533.0 ± 600.8 mm^3 compared with at T1, while BV had decreased by 8.1 ± 274.0 mm^3 in group II (p = 0.002). The relative changes in BV were 19.5 ± 24.2% and 0.4 ± 11.6% in groups I and II, respectively (p = 0.007), which signified the occurrence of more active bone regeneration in group I.

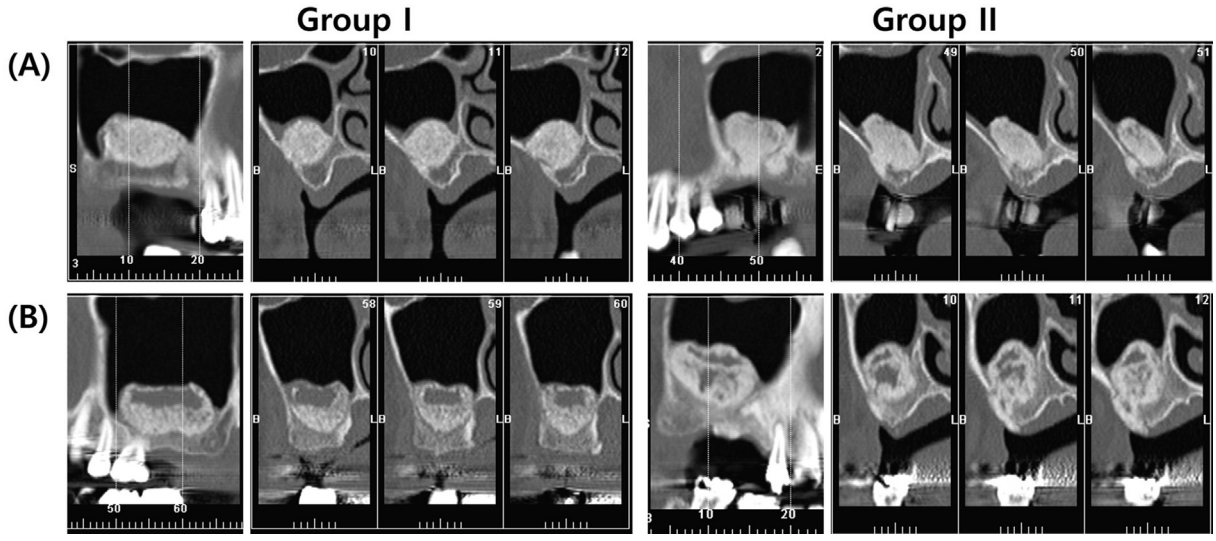

Fig. 4. Void formation at T1 in each group, showing an example case with the VV not exceeding 20% of the TV (A) and one with the VV exceeding 20% of the TV (B).

Table 2
Absolute and relative volumes of the three considered parameters for groups I and II at T1 and T2.

	T1			T2			T1 vs T2 (*p*-value)	
	Group I	Group II	*p*-value	Group I	Group II	*p*-value	Group I	Group II
TV (mm^3)	4113.5 ± 1276.5	2951.0 ± 734.7	0.014	4065.9 ± 1288.8	2834.0 ± 782.5	0.006	0.600	0.084
BV (mm^3)	2962.0 ± 667.0	2578.7 ± 680.6	0.174	3495.0 ± 894.5	2570.6 ± 677.5	0.014	0.002	0.754
BV (%)	75.4 ± 17.1	87.3 ± 6.0	0.073	87.5 ± 7.9	91.0 ± 3.9	0.277	0.001	0.028
VV (mm^3)	1151.5 ± 983.1	372.3 ± 180.9	0.057	570.9 ± 503.3	263.4 ± 157.3	0.115	0.002	0.019
VV (%)	24.6 ± 17.1	12.7 ± 6.0	0.073	12.5 ± 7.9	9.0 ± 3.9	0.277	0.001	0.028

Data are presented as mean ± standard deviation.
Statistics between groups I and II are based on the Wilcoxon rank-sum test; those between T1 and T2 are based on the Wilcoxon signed-rank test. *p*-values of less than 0.05 were considered to be statistically significant.
T1, 3-month follow-up; T2, long-term follow-up (at least 24 months); TV, total volume; BV, bone volume; VV, void volume.

Table 3
Volumetric changes for groups I and II over time.

	Group I	Group II	*p*-value
TV (mm^3)	−47.6 ± 499.4	−117.0 ± 229.5	0.514
TV (%)	0.1 ± 15.7	−4.2 ± 7.4	0.355
BV (mm^3)	533.0 ± 600.8	−8.1 ± 274.0	0.002
BV (%)	19.5 ± 24.2	0.4 ± 11.6	0.007
VV (mm^3)	−580.6 ± 627.0	−108.9 ± 148.1	0.026
VV (%)	−41.9 ± 28.9	−26.5 ± 26.6	0.103

Data are presented as mean ± standard deviation.
Statistics between groups I and II are based on the Wilcoxon rank-sum test. *p*-values of less than 0.05 were considered to be statistically significant.
See Table 2 for abbreviations.

4. Discussion

This study was designed to analyze volumetric changes in void space and newly formed bone after MSFA with rhBMP-2 or ABX, and to evaluate the long-term efficacy of bone regeneration using rhBMP-2 in MSFA compared with MSFA with ABX. Even though there was no difference in the amount of graft material used, group I with rhBMP-2 initially showed a larger TV than group II with ABX, which was due to the dispersed graft materials and a larger VV. Over time, the dispersed graft materials did not condense again, and the TV was maintained in the long term. The VV in group I gradually decreased and the BV increased. As a result, the BV at T2 was significantly greater in group I than in group II (Fig. 5).

In previous studies using rhBMP-2 for MSFA, bone formation has been evaluated by two-dimensional CT analysis, which measures the height of the augmented maxillary sinus, or by histological analysis (Boyne et al., 2005; Triplett et al., 2009; Kao et al., 2012; Froum et al., 2013; Kim HJ et al., 2015; Kim MS et al., 2015). In addition, previous studies generally have had a follow-up period of only 3–9 months, with only early new bone formation being assessed (Boyne et al., 2005; Triplett et al., 2009; Kao et al., 2012; Froum et al., 2013; Kim HJ et al., 2015; Kim MS et al., 2015). Thus, the long-term changes in augmented space after MSFA with rhBMP-2 were analyzed three-dimensionally for the first time in this study.

There are only two previous clinical reports of internal void formation after MSFA (Tsai et al., 2015; Kang et al., 2016). Tsai et al. evaluated two-dimensional CT sections, and reported voids of 2.07–8.51% of the augmented area after MSFA using beta-tricalcium phosphate (β-TCP) (Tsai et al., 2015). Kang et al. (2016) reported a case of MSFA where the TV increased by 1764.7 mm^3 over the first 6 months after MSFA, using HA/β-TCP mixed with rhBMP-2 (Kang et al., 2016). Voids are not formed immediately after surgery but instead develop early in the postoperative period. Although this case did not suggest a definite void volume, the increase in TV was explained by the internal void formation (Kang et al., 2016). In our study, the void space after MSFA was measured three-dimensionally. The void formation was observed as 24.6 ± 17.1% in the BMP-2/H group and 12.7 ± 6.0% in the ABX group; this was because the implanted HA granules usually showed uneven distribution along the edges of the elevated space in the BMP-2/H group, while the sinus was densely packed with the graft material at T1 in the ABX group.

Voids are known to occur after MSFA because of the difficulty in condensing the graft material, as a result of the limited surgical field and the open-ended posterior region of the space under the elevated maxillary sinus membrane (Tsai et al., 2015). It has been suggested that void formation can be caused by tissue insult, tissue inflammation, the body's defense mechanisms, and/or a delayed hypersensitivity inflammatory reaction (Wikesjö et al., 2004; Shahlaie and Kim, 2008). Increased void formation after MSFA in the BMP-2/H group seems to be related to increased soft tissue swelling in patients (Kim HJ et al., 2015); notably, a large amount of seroma occurred in response to the use of rhBMP-2 in a rat spinal arthrodesis model (Hsu et al., 2013). Unexpected complications such as extensive swelling, seromas, and cyst-like void formation may be related to the dose of rhBMP-2. Empty vacuoles without a distinct matrix were formed around implants coated with a high dose of rhBMP-2 in dogs (Wikesjö et al., 2004). However, the relationship between the dose of rhBMP-2 and void formation in MSFA has not yet been elucidated. Thus, further clinical studies should be conducted to find the appropriate dose of rhBMP-2 required to promote bone formation and minimize void formation.

In MSFA with rhBMP-2, different results have been observed, depending on what was used as the carrier of rhBMP-2. For example, the first randomized controlled clinical trial of rhBMP-2 for MSFA and its subsequent clinical multicenter study used an absorbable collagen sponge (ACS) as a carrier of rhBMP-2, while autogenous graft alone or a mixture of autograft and allograft were used in the control group (Boyne et al., 2005; Triplett et al., 2009). Boyne et al. (2005) reported that the alveolar bone width at the one-fourth area of the alveolar crest was significantly larger in the control group compared with the rhBMP-2/ACS group at 4 months after MSFA. Similarly, Triplett et al. (2009) reported that the mean change in bone height in the control group was 9.46 ± 4.11 mm, which was significantly larger than that in the rhBMP-2/ACS group (7.83 ± 3.52 mm). On the other hand, the density of the new bone in the rhBMP-2/ACS group was initially lower than that of the control group, but gradually increased to be comparable to or denser than that of the control group at 6 months after dental restoration (Boyne et al., 2005; Triplett et al., 2009).

When ABX was used as a carrier of rhBMP-2, new bone formation was reported to be significantly lower at 6–9 months after surgery compared with the ABX-only group (16.04 ± 7.45% vs 24.85 ± 5.82%) (Kao et al., 2012). Therefore, the incorporation of rhBMP-2 by ABX should be treated with caution (Torrecillas-Martinez et al., 2013). In a study by Kim MS et al. (2015), BCP was grafted with rhBMP-2, and there were no significant differences in

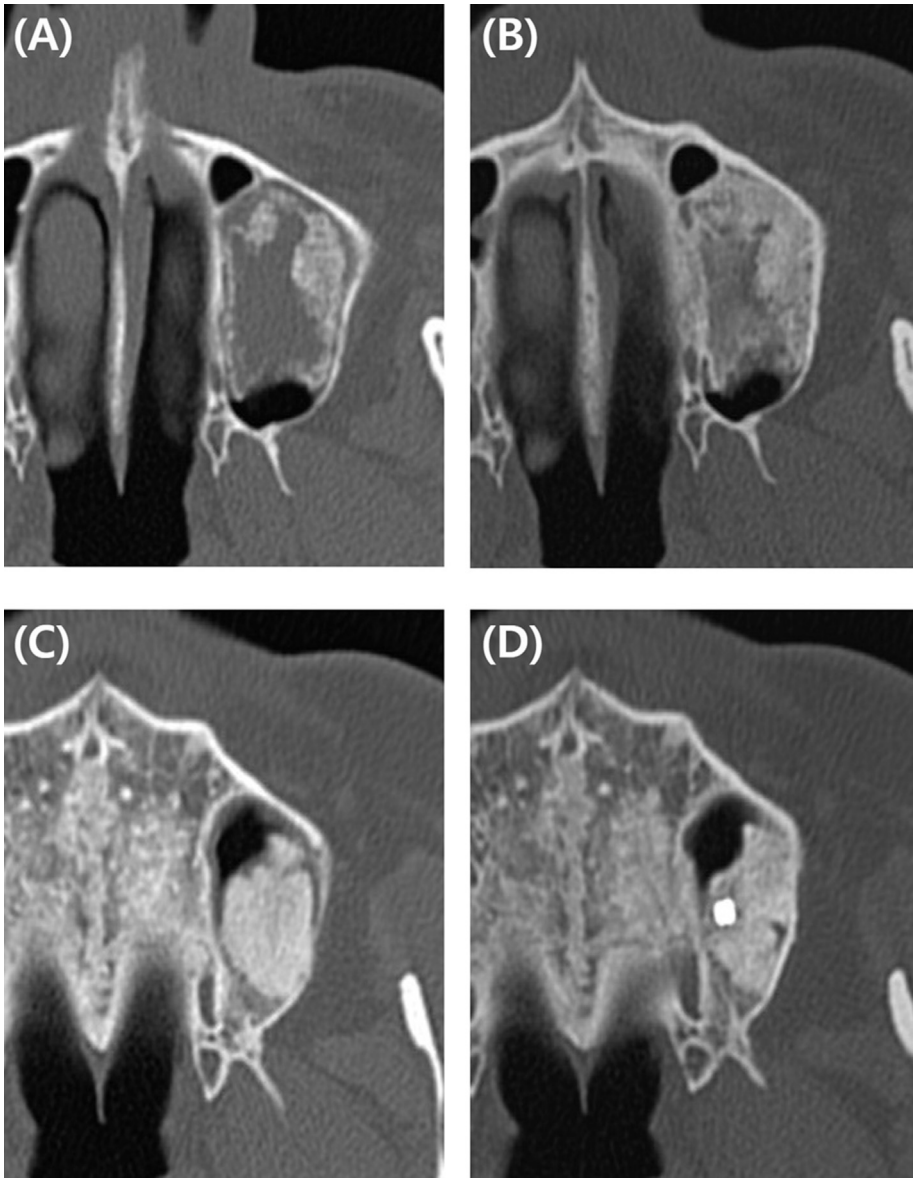

Fig. 5. CT axial sections of a representative case from each group. Group I at T1 (A), group I at T2 (B), group II at T1 (C), and group II at T2 (D).

volumetric changes when comparing immediately after surgery with six months follow-up. However, there was also no significant difference in new bone formation between BCP with rhBMP-2 and ABX alone in histomorphometric analysis of biopsied specimens; therefore, it seems that there was no effect of rhBMP-2 on the volumetric changes seen at 6 months in that study. In a rabbit MSFA study using rhBMP-2 and BCP, a void in the central area was observed 2 weeks postoperatively but was uniformly substituted by bone at 8 weeks (Choi et al., 2013). In one clinical case, it was reported that voids were partially replaced by new bone in CT images taken at 26 months after MSFA (Kang et al., 2016). When allogenic bone was used as a carrier of rhBMP-2, there was no difference in bone formation in comparison with the control group, which used allogenic bone alone (Froum et al., 2013), while bone formation in the group with rhBMP-2 delivered by HA was significantly increased at 3 months versus the ABX control group (16.10 ± 10.52% vs 8.25 ± 9.47%) (Kim HJ et al., 2015). HA as a carrier for rhBMP-2 has been reported to improve the fusion rate when used in an animal study on spine fusion (Lee et al., 2012).

In our study, HA granules were used as a carrier for rhBMP-2, which had a similar particle and pore size and a similar material architecture to ABX. There was no significant change in TV in either the BMP-2/H or ABX group from 3 months to at least 24 months after surgery. The BV of the BMP-2/H group was not significantly different from that of the control group at 3 months. Over time, VV showed a tendency to decrease and BV tended to increase. These changes were statistically significant in the BMP-2/H group. In the long-term follow-up period of at least 24 months, the BMP-2/H group had a BV of 3495.0 ± 894.5 mm^3, which was significantly greater than that of the ABX group, at 2570.6 ± 677.5 mm^3. The increase in bone formation in the BMP-2/H group might be attributed to an effect of the sustained-released of rhBMP-2.

The ABX used for the control group (group II) was bovine HA (Bio-Oss®; Geistlich Pharma AG, Wohlhausen, Switzerland), which has a naturally porous trabecular architecture and a fine crystalline structure; its interconnecting macro- and micropores promote revascularization and migration and subsequent attachment of osteogenic cells (Piattelli et al., 1999; Bassil et al., 2013; Lee et al.,

2016). ABX has been widely applied in MSFA and is known to experience a small volume reduction after MSFA (Jensen et al., 2012a; Mazzocco et al., 2014; Umanjec-Korac et al., 2014; Lutz et al., 2015; Gultekin et al., 2016a, b). In addition, ABX has often been used as a comparable biomaterial in animal and clinical studies (Jung et al., 2003; Lee et al., 2006, 2017; Bassil et al., 2013). ABX after MSFA has shown volume reductions of 8–10% over 6–9 months of follow-up, and of 19.3% after 2 years (Mazzocco et al., 2014; Umanjec-Korac et al., 2014; Gultekin et al., 2016a, b). ABX mixed with other graft materials has been used to compensate for the disadvantages of materials that absorb more significantly after MSFA (Jensen et al., 2012a; Kim et al., 2013; Gultekin et al., 2016a). Jensen et al. (2012b) reported that volume reduction was inversely proportional to the amount of ABX mixed with autogenous bone used for MSFA in animal experiments. In our study, the TV of the ABX group was well maintained, without any significant change during the observation period of 24 months or more, while the VV within MSFA decreased and the BV increased over time.

5. Conclusion

In our clinical study, the volumetric changes of MSFA in the long-term were evaluated and the bone-forming pattern in the BMP-2/H group was compared with that in the control group with ABX alone, using 3D CT analysis. When MSFA was performed with BMP-2/H, the TV increased initially and was accompanied by void formation. It was observed that osteogenesis progressed to the internal void space without changing the TV over time. Therefore, rhBMP-2 is effective for long-acting bone regeneration after MSFA.

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Conflicts of interest

The authors have no financial interests to declare in relation to the content of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcms.2019.07.016.

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