의학박사 학위논문

인간 재조합 골형성 단백질-2가 상악동 골이식 후 식립한 임플란트에 미치는 영향

Effect of recombinant human bone morphogenic protein-2 on the implant placed in the grafted maxillary sinus

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이 논문을 의학박사 학위 논문으로 제출함

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Abstract

Introduction: This study aimed to compare 3- and 5-year survival rates and marginal bone loss (MBL) for implants placed in a grafted maxillary sinus using recombinant human bone morphogenetic protein-2 (rhBMP-2) during functional loading.

Materials and methods: This retrospective study analyzed 63 implants from 45 patients, who underwent maxillary sinus floor augmentation (MSFA), with or without rhBMP-2, between January 2016 and April 2019. The outcome variables were 3- and 5-year cumulative survival rates of the implants and MBL after functional loading. Other variables assessed included patient demographic information, preoperative residual bone height (RBH), surgical site, implant length and diameter, graft material, healing period before loading, prosthetic type, opposing dentition, and crown-to-implant ratio. Comparisons were performed using the chi-squared test or Fisher's exact test for categorical variables, and Student's *t*-test for continuous variables.

Results: The cumulative 3- and 5-year survival rates of the implants were 100% and 100% in the rhBMP-2 group and 95.5% and 86.4% in the non-rhBMP-2 group, respectively. The mean (±standard deviation) 3- and 5-year MBL were 1.14 ± 0.67 mm, 1.30 ± 0.74 mm in the rhBMP-2 group and 1.68 ± 0.90 mm, 2.27 ± 1.29 mm in the non-rhBMP-2 group, respectively; these differences were statistically significant.

Conclusion: Placing dental implants with MSFA using rhBMP-2 was favorable in terms of implant survival and MBL when preoperative RBH was <5 mm.

Keywords: marginal bone loss, rhBMP-2, sinus graft, survival rate

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Introduction

Resorption of the alveolar ridge and the maxillary sinus pneumatization make implant placement in the maxillary sinus challenging after dental extraction. Increasing osteoclastic activity within the Schneiderian membrane causes expansion of the maxillary sinus and promotes atrophy of the alveolar bone. Additionally, the edentulous posterior maxilla has a soft, low bone density which results in low resistance during this process. Recently, maxillary sinus floor augmentation (MSFA) has been performed in order to prepare implant sites that have a decreased vertical bone height.

Many studies have reported that recombinant human bone morphogenetic protein-2 (rhBMP-2) accelerates bone formation and demonstrates osteoinductive potential.[1] Bone morphogenetic proteins (BMPs) belong to the superfamily of transforming growth factor beta (TGF-β) and comprise >20 various types.[2] Among these, BMP-2, BMP-4, BMP-5, BMP-6, and BMP-7 are known to promote bone formation, and rhBMP-2 is widely used in the field of maxillofacial surgery.[3] The process of generating rhBMP-2 through genetic recombination involves the expression of Chinese hamster ovary cells, mammalian cells, or *Escherichia coli* via the recombination of complementary DNA. However, when graft materials are mixed with rhBMP-2, a significant amount of rhBMP-2 may be lost in the body. Therefore, a carrier is needed to bind rhBMP-2 and release BMPs to the target cell population.[4] Graft materials were used as carriers for rhBMP-2 in this study. However, it is unclear how BMP affects implants in the grafted maxillary sinus. As such, this study aimed to compare the 3- and 5-year survival rates and marginal bone loss (MBL) of implants placed in a grafted maxillary sinus using rhBMP-2 during functional loading.

Materials and Methods

Study design and sample

This retrospective study analyzed 63 implants from 45 patients who underwent MSFA, with or without rhBMP-2, between January 2016 and April 2019. Data were collected from surgical records, panoramic radiographs, and cone-beam computed tomography (CBCT) images. The inclusion criteria for this study were implants with <5 mm of preoperative residual bone height (RBH) and the availability of preoperative radiographs to measure RBH, immediate postoperative radiographs, as well as radiographs captured before or after functional loading. Patients with uncontrolled diabetes or maxillary sinusitis, and those with incomplete medical records were excluded. Implants were divided into two groups, based on whether rhBMP-2 was used.

Study variables

The outcome variables were the 3- and 5-year cumulative survival rates of the implants and MBL after functional loading. Other variables assessed included patient demographic information, preoperative RBH, surgical site, implant length and diameter, graft material, healing period before loading, prosthetic type, opposing dentition, and the crown-to-implant ratio. Patient demographic information was obtained from both medical and surgical records. To measure preoperative RBH, the point corresponding to the center of each inserted implant was measured on preoperative panoramic radiographs. On follow-up panoramic radiographs, MBL was determined as the distance between the implant-abutment junction and the most coronal level of bone-to-implant contact at the mesial and distal sides of each implant.

Surgical procedure

All surgical procedures were performed using the lateral window technique for the maxillary sinus under local anesthesia. In the rhBMP-2 group, 0.25 mg of rhBMP-2 (Novosis, CGBio, Seoul, Korea) dissolved in 0.5 mL of

normal saline was mixed with the graft material. Deproteinized bovine bone with spongiosa granules (Bio-Oss, Geistlich, Wolhusen, Switzerland), freeze-dried cancellous bone (Allobone, CGBio, Seoul, Korea), intraoral autograft (i.e., mandibular ramus), and their mixtures were used as appropriate. The collagen membranes (Ossguide, Bioland, Chungcheongbuk-do, Korea) were used to cover the sinus windows. Implants (Osstem, Gyeonggi-do, Korea) were installed simultaneously with MSFA whenever possible.

Statistical analysis

Variables were evaluated using descriptive analysis. Categorical variables are expressed as frequency with a percentage, while continuous variables are expressed as mean ± standard deviation (SD). Comparisons were performed using Fisher's exact test or the chi-squared test for categorical variables, and Student's *t*-test for continuous variables. Kaplan–Meier analysis was performed to identify differences in the cumulative survival rate of the implant between the two groups. Differences with $P < 0.05$ were considered to be statically significant.

Results

Sixty-three implants in 45 patients (19 male, 26 female) fulfilled the inclusion criteria. The mean age of the rhBMP-2 and non-rhBMP-2 groups was 60.9 ± 11.9 and 59.4 ± 7.83 years, respectively. The mean preoperative RBH was 3.62 ± 1.14 mm and 3.31 ± 1.10 mm in the in the rhBMP-2 and non-rhBMP-2 groups, respectively. Characteristics of patients in the rhBMP-2 and non-rhBMP-2 groups, including demographic information, surgical site, period of prosthetic loading are summarized in Table 1. Other parameters, such as preoperative RBH, healing period before loading, crown-to-implant ratio, methods of implant placement (simultaneous /staged), prosthetic type (single/splinted), and state of the opposing dentition are summarized in Table 2. No significant differences in the other variables were observed between the groups (P >0.05). In the rhBMP-2 group, 28 implants reached functional loading in 3 years and 11 implants reached functional loading in 5 years. In the non-rhBMP-2 group, 32 implants reached functional loading in 3 years and 21 implants reached functional loading in 5 years. In the non-rhBMP-2 group, 3 implants were lost at 2, 55, and 57 months (3.48, 3.6, and 3.46 mm of preoperative RBH, respectively) after prosthetic loading. In contrast, no implants were lost in the rhBMP-2 group. Although not statistically significant, the cumulative 3- and 5-year survival rates for the implants were 100% and 100% in the rhBMP-2 group and 95.5% and 86.4% in the non-rhBMP-2 group, respectively (Figure 1). The mean 3- and 5-year MBL were 1.14 ± 0.67 mm, 1.30 ± 0.74 mm in the rhBMP-2 group and 1.68 ± 0.90 mm, 2.27 ± 1.29 mm in the non-rhBMP-2 group, respectively, and the differences were statistically significant (P <0.05).

Table 1. Patient demographics and clinical data

	Sex(M/F)	Age(year)	Surgical site (P1/P2/M1/M2)	Period of functional loading(months)
rhBMP-2	9/14	60.9 ± 11.9	2/2/13/11	52.9 ± 11.5
Non-rhBMP-2	10/12	59.4 ± 7.83	0/1/17/17	60.7 ± 11.1

Abbreviations: M, male; F, female; P1, first premolar; P2, second premolar; M1, first molar; M2, second molar; rhBMP-2, recombinant human bone morphogenetic protein-2.

Table 2. Clinical data according to other parameters.

	rhBMP-2 (N=28)	Non-rhBMP-2 (N=35)	*P*
Preoperative RBH(mm)	3.62 ± 1.14	3.31 ± 1.10	0.289
Staged or simultaneous			
Staged	3(10.7)	4(12.5)	1.000
Simultaneous	25(89.3)	28(87.5)	
Healing period	8.14 ± 2.07	8.31 ± 2.01	0.749
Opposite dentition			
Natural dentition	15(53.6)	18(56.3)	0.835
Implant	13(46.4)	14(43.8)	
Prosthetic type			
Single	4(14.3)	4(12.5)	1.000
Splinted	24(85.7)	28(87.5)	
Crown-implant ratio	1.23 ± 0.30	1.34 ± 0.23	0.147
3-year MBL	1.14 ± 0.67	1.68 ± 0.90	0.012*
5-year MBL	1.30 ± 0.74 (N=11)	2.27 ± 1.29 (N=21)	0.029*

Abbreviations: RBH, residual bone height; rhBMP-2, recombinant human bone morphogenetic protein-2; MBL, marginal bone loss. *P<0.05

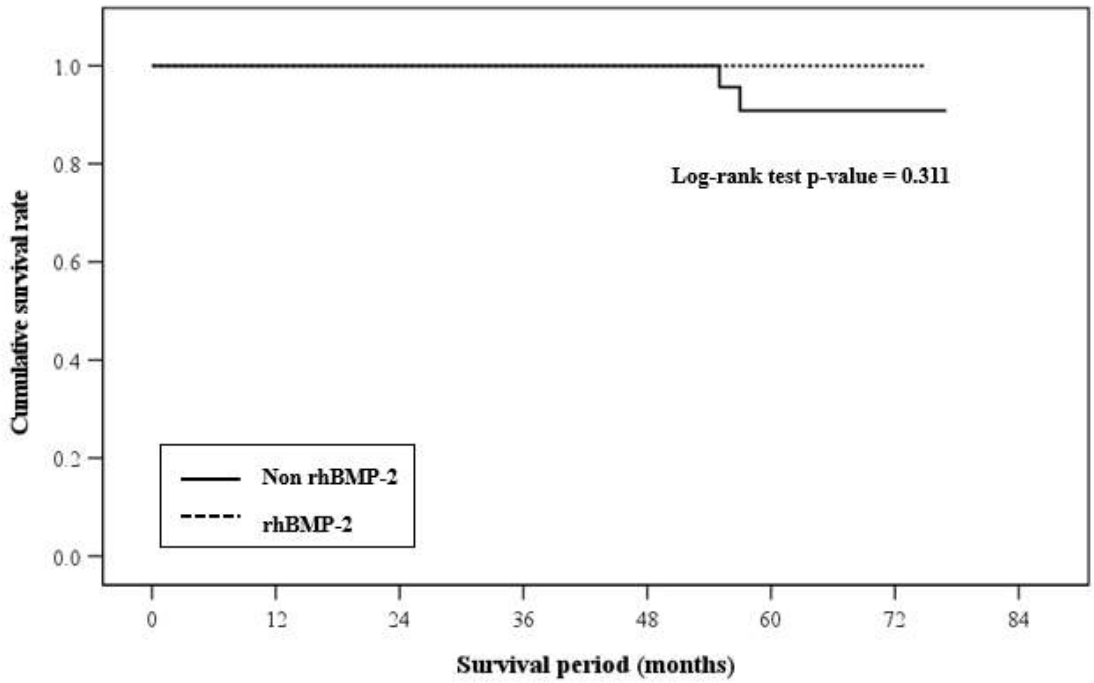

Figure 1. Kaplan-Meier cumulative survival rates

Abbreviation: rhBMP-2, recombinant human bone morphogenetic protein-2.

Discussion

This study evaluated the effect of rhBMP-2 on MSFA by analyzing 3- and 5-year implant survival rates and MBL. Although not statistically significant, the 3- and 5-year implant survival rates were 100% in the rhBMP-2 group and 95.5% and 86.4%, respectively, in the non-rhBMP-2 group. However, the differences in the 3- and 5-year MBL between the two groups were statistically significant. (P <0.05).

Autograft is considered the gold standard for bone healing due to its osteoblast content and ability to produce predictable outcomes. However, it is associated with complications such as infection and bone resorption at the donor site.[5] Although allografts have osteoinductive effects, their ability to stimulate bone regeneration is limited.[6] Because xenografts have limited osteoinductive ability, their capacity to form bones is slow and inadequate.[7] Many clinical trials have been conducted in order to overcome these problems. BMPs were first described by Urist in 1965,[8] and Wozney produced BMP-2 and BMP-4 using genetic recombination in 1988.[9] rhBMP-2 produced through a recombinant process has shown the highest osteoinductivity compared to other BMPs. BMP-2 induces differentiation in various cell types, including osteoblasts, chondrocytes, neuronal cells, cancer cells, and endothelial cells.[10] When the BMP-2 receptor type I/II serine/threonine kinase is activated, BMP-2 activates the Smad pathway.[11] This signaling system promotes bone formation by increasing the expression of RUNX2, Dlx5, and Osterix, which leads to the differentiation of mesenchymal stem cells into osteoblasts.[11] Differentiated osteoblasts produce the bone matrix and secrete alkaline phosphatase, which deposits calcium phosphate in collagen structures and generates hydroxyapatite.[11] Additionally, BMP-2 induces angiogenesis in human endothelial progenitor cells by stimulating integrin α6 expression.[10]

However, BMP requires a carrier since BMPs easily diffuse and could be lost in body fluids. To ensure the differentiation of mesenchymal cells, the delivery system for BMP must be sustainable, allowing the requisite cytokines to exert their effects. According to Manocha et al., the delivery of BMP without a carrier did not sustain for more than a few hours at the graft site.[12] Therefore, the binding affinity of BMP to a carrier is likely critical. Many studies have demonstrated that rhBMP-2 combined with autogenous bone or bone substitutes can achieve predictable results,

although it is questionable which carrier is more favorable.[13,14,15] In this study, autogenous bone and/or bone substitutes were used as carriers for rhBMP-2.

Several studies have reported that the survival rates[16] and MBL around implants placed in the augmented maxillary sinus are influenced by RBH. As preoperative RBH decreases, previous studies have shown that the implant survival rate also decreases.[16,17] Rosen et al. reported an implant survival rate of 96% when the RBH was ≥5 mm and 85.7% when the RBH was ≤4 mm.[17] Khouly et al. reported a 90% cumulative implant survival rate after a mean follow-up of 7.2 years.[18] Additionally, they found that implants placed with RBH ≥5 mm had greater implant survival compared to those placed with RBH <3 mm.[18] Moreover, Bjarni et al. reported that survival was 91.3% for implant sites with RBH ≤4 mm, 90% for sites with 4 mm and 5 mm, which was compared to 100% in sites with RBH >5 mm.[19] Misi Si et al. reported that the implant survival rate was significantly lower when the RBH was <5 mm.[20] According to Gonzalez et al., MBL was 0.07 mm at an RBH ≥4 mm and 0.55 mm at an RBH ≤4 mm over an average of 29.7 months after the alveolar crestal approach.[21] In a previous study using a multivariate model, RBH <5 mm was identified as a risk factor for long-term implant survival.[22] Therefore, in the present study, implants with <5 mm of RBH were established as the inclusion criterion.

In this study, a low dose of rhBMP-2 (0.25 mg) was mixed with graft material in the rhBMP-2 group, which led to a significantly lower MBL compared to the non-rhBMP-2 group. This suggests that a low dose of BMP-2 promotes bone formation around implants with unfavorable RBH by enabling earlier mineralization, thus improving the mechanical stability and function of the implant. Several studies have demonstrated that a low-doses of rhBMP-2 result in early bone formation. Chao et al. reported significantly higher and quicker new bone formation in a large animal model with the use of low-dose rhBMP-2 (0.2 mg/mL), exhibiting early mineralization and bone growth extending to the implant platform.[23] Patricia et al. described that low-dose rhBMP-2 demonstrated significant capacity for bone regeneration in pigs with mandibular continuity defects.[24] Tsuji et al. reported that in mice lacking BMP-2 and having limb fractures, the early stages of fracture healing seem to be hindered and in mice with the ability to produce BMPs, levels of BMP-2, BMP-4, and BMP-7 were elevated early after the fracture.[25]

Efficient dispersion of occlusal load is important for the long-term success of the implant and the type of prosthesis and the condition of opposing dentitions should be taken into consideration.[26] Implants and natural teeth respond differently to occlusal forces due to the absence of a periodontal ligament in implants. Excessive occlusal force, unlike natural teeth, can lead to implant failure due to osteointegration breakdown or microfractures at the implant-bone interface.[26] Splinting the prosthetic component in implants increases the support tissue's surface area and effectively distributes occlusal load among the implants.[27]

An increase in the crown-to-implant ratio can cause MBL due to the overload and non-axial load induced by the leverage effect.[28] In a finite element analysis of 889 single-tooth implant cases, a survival rate of 98.2% was reported for a crown-to-implant ratio of 1.3:1.[29] Hingsammer et al. examined 74 implants and reported that bone absorption did not increase unless the crown-to-implant ratio was greater than 1.7.[30]

Several variables are known risk factors that affect implants. To limit the impact on implant survival and MBL to rhBMP-2 in this study, other variables were examined to determine whether there were any differences between the groups, with none observed (P >0.05).

This study had some limitations, the first of which was its small sample size and retrospective design. Although implant survival was higher in the rhBMP-2 group compared to the non-rhBMP-2 group, this difference was not statistically significant. This lack of statistical significance could be attributed to either the small sample size or the number of implant failures. Additionally, the medical records did not provide further information about the presence of detrimental parafunctions, such as night bruxism and clenching. Despite its limitations, the results of this study suggest that adding rhBMP-2 to graft materials has a positive impact on implant placement in the grafted maxillary sinus, considering implant survival and MBL when the preoperative RBH is <5 mm. This was evident due to the strong osteogenic potential and early mineralization exhibited by rhBMP-2, thereby enhancing the bone-implant contact area compared to the non-rhBMP-2 group.

However, risk factors associated with MBL are likely multifactorial, including pre-existing diseases such as autoimmune diseases, diabetes, and periodontitis, heavy smoking (>15 cigarettes/day), implant location, and insertion torque.[31] Therefore, future research should conduct multiple

analytical comparisons.

Conclusion

Adding rhBMP-2 to bone graft materials in the grafted maxillary sinus was favorable in terms of implant survival and MBL when the preoperative RBH was <5 mm.

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국문요약

목적: 본 연구는 상악동 골이식 시 rhBMP-2를 골 이식재와 함께 사용한 군과 사용하지 않은 군의 임플란트 생존율과 변연골 소실을 비교하는 것이다.

방법: 울산대학교병원에 내원하여 2016년 1월부터 2019년 4월까지 rhBMP-2를 사용하거나 사용하지 않고 상악동 골이식 후 식립한 63개의 임플란트, 45명의 환자를 대상으로 하였다. 결과 변수들은 기능 부하 후 1) 임플란트의 3년, 5년 누적 생존율, 2) 변연골 소실이다. 기타 변수들은 환자의 인구 통계학적 요인, 수술 전 잔존골 높이, 식립 위치, 임플란트 길이와 직경, 골이식 재료, 부하를 가하기 전 치유 기간, 보철물 유형, 대합치 상태를 비교 조사하였다.

결과: 임플란트의 3년, 5년 누적 생존율은 rhBMP-2 그룹에서 100%, non-rhBMP-2 그룹에서 각각 95.5%, 86.4%였다. 평균 3년, 5년 변연골 소실은 rhBMP-2 그룹에서 각각 1.14 ± 0.67mm, 1.30 ± 0.74mm, non-rhBMP-2 그룹에서 각각 1.68 ± 0.90mm, 2.27 ± 1.29mm 였다. 두 그룹 사이에 3년과 5년에서 통계적으로 유의미한 차이가 있었다.

결론: 수술 전 잔존골 높이가 5mm 미만으로 불량할 때 상악동 골이식술 시 골이식재에 rhBMP-2를 첨가하는 것은 임플란트 생존율과 변연골 소실 관점에서 유리하다.