Does the Addition of Bone Morphogenetic Protein 2 to Platelet-Rich Fibrin Improve Healing After Treatment for Medication-Related Osteonecrosis of the Jaw?

Jung-Hyun Park, DDS, PhD, *Jin-Woo Kim, DDS, PhD,† and Sun-Jong Kim, DDS, PhD‡*

Purpose: To investigate the effect of the addition of bone morphogenetic protein 2 (BMP-2) to leukocyte-rich and platelet-rich fibrin (L-PRF) on the treatment of medication-related osteonecrosis of the jaws (MRONJ), this study compared the healing outcome of combined use of BMP-2 and L-PRF with single use of L-PRF.

Patients and Methods: Of 55 patients who were diagnosed with MRONJ, 25 were treated with L-PRF alone and 30 were treated with L-PRF and recombinant human BMP-2. For each patient, surgical sites were evaluated postoperatively at 4 and 16 weeks. Associations between the treatment method and the resolution of MRONJ were analyzed with the adjustment of patient-specific factors that may influence the treatment outcome.

Results: At 4 and 16 weeks postoperatively, patients with MRONJ who were treated with both L-PRF and BMP-2 showed favorable outcomes with complete resolution of the lesions, which was statistically significant compared with that of the therapy using L-PRF alone ($P = .028$). Therefore, the additional use of BMP-2 considerably improved MRONJ healing. Among patient-specific factors, the existence of a bacterial colony in the biopsy specimen was a significant factor that negatively affected disease resolution ($P = .017$).

Conclusions: The combined use of BMP-2 and L-PRF leads to the early resolution of MRONJ; thus patients who need to continue antiresorptive therapy may benefit from the combined regimen.

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Antiresorptive medicines, such as bisphosphonates, are widely used to treat various bone diseases, ranging from osteoporosis to metastatic bone disease.[1] Long-term antiresorptive therapy is known to be associated with the serious complication of medication-related osteonecrosis of the jaws (MRONJ).[2] This occurs in patients who have been receiving or have been exposed to antiresorptive or antiangiogenic agents with no history of radiation therapy to the maxillofacial region. The lesion is characterized by exposed

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*Clinical Assistant Professor.

†Clinical Assistant Professor.

‡Professor.

Jung-Hyun Park and Jin-Woo Kim contributed equally to this study.

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Address correspondence and reprint requests to Dr S-J Kim: Department of Oral and Maxillofacial Surgery, Ewha Womans University, Mok-Dong Hospital, Mok 5-dong, Yangcheon-gu, Seoul 158-710, Republic of Korea; e-mail: oralsurgeonsj@gmail.com

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necrotic bone in the maxillofacial area, which has persisted for more than 8 weeks.[2] Although the first MRONJ case was reported over a decade ago,[3] the pathophysiology of the disease is still unclear.[4] Proposed hypotheses include oversuppression of bone remodeling,[5,6] angiogenesis inhibition,[7-10] and direct toxicity on the oral mucosa.[11-13]

Although MRONJ adversely affects quality of life as a result of considerable morbidity, there is no definitive standard treatment for MRONJ.[14] Among the proposed therapeutic protocols, autologous platelet concentrate (APC) is known to be an effective adjunct in treating MRONJ.[15] Because APC contains high concentrations of protein growth factors secreted by platelets including platelet-derived growth factor, transforming growth factor β, vascular endothelial growth factor, and endothelial growth factor,[16] it has been reported to stimulate and accelerate tissue healing. The first clinical report on the use of APC in the treatment of MRONJ[17] led to publications of many subsequent clinical studies regarding the topic.[15,18-20] Because of the absence of bone morphogenetic proteins (BMPs) within APCs, however, there have been controversies over whether APCs are effective for the treatment of MRONJ, which is primarily thought to be an osseous disease.[16,21]

Recently, there have been studies on the use of bone morphogenetic protein 2 (BMP-2) for the treatment of MRONJ to increase bone remodeling.[22,23] BMP-2, a member of the transforming growth factor β superfamily, has been widely used for the treatment of bone defects because of its osteoinductive property.[24] Oversuppression of bone remodeling is thought to be one of the main pathogeneses of MRONJ because the main pharmacologic effect of bisphosphonates and other antiresorptive drugs is inhibition of osteoclasts.[5,6] Therefore, BMP-2 has been thought to have a potential reversal effect on the remodeling-suppressed bone in MRONJ, which is bone remodeling enhancement.[23]

On the basis of previous studies, we hypothesized that simultaneous application of APC and BMP-2 stimulates not only soft tissue healing but also bone remodeling, thus contributing to the successful treatment of MRONJ. There is a lack of research on the simultaneous application of APC and BMP-2 in the treatment of MRONJ. To investigate the effect of the addition of BMP-2 to APC on the treatment of MRONJ, this study compared the healing outcome of combined use of BMP-2 and leukocyte-rich and platelet-rich fibrin (L-PRF) with single use of L-PRF. In this study L-PRF was used as an APC. The association between MRONJ resolution and patient-specific factors that may influence the treatment outcome of MRONJ also was adjusted and analyzed.

Patients and Methods

This study followed the Declaration of Helsinki (2000) on medical protocol and ethics and was approved by the Institutional Review Board of Ewha Medical Center, Seoul, Republic of Korea. All participants provided written informed consent.

A prospective study was performed by enrolling MRONJ patients who visited the Department of Oral and Maxillofacial Surgery at Ewha Womans University Medical Center between 2012 and 2015. The inclusion criteria were *1)* patients who were receiving current treatment or received previous treatment with antiresorptive agents, *2)* exposed bone or bone that could be probed through an intraoral or extraoral fistula in the maxillofacial region that had persisted for longer than 8 weeks based on the American Association of Oral and Maxillofacial Surgeons (AAOMS) MRONJ definition,[2] and *3)* a radiographically confirmed destructive bony lesion with sequestra or clinically confirmed necrotic bone in the jaw that needed to be surgically removed. Patients were excluded if they had a history of radiation therapy to the jaws or metastatic disease of the jaws according to the definition provided by the AAOMS.[2]

The site and size of the exposed necrotic bone; presence of an intraoral or extraoral fistula; and presence of mucosal erythema and swelling, purulent drainage, and pain associated with the lesion were evaluated clinically. All patients also were screened radiographically with panoramic views, computed tomography, and bone scanning to assess the extension of lesions. Information related to antiresorptive therapy was collected, including the type of antiresorptive agents taken, duration of antiresorptive therapy, route of administration, and reason for antiresorptive therapy. Through medical and dental history taking, dental etiologic factors and other risk factors for MRONJ development, such as corticosteroid use and diabetes, were examined. When patients were diagnosed with MRONJ, blood was drawn to examine the serum concentration of C-terminal cross-linked telopeptide of type I collagen (sCTX) (electro-chemiluminescence immunoassay with β-CrossLaps/Serum; Roche Diagnostics, Basel, Switzerland).

Staging of the lesions was performed according to the AAOMS clinical classification of MRONJ[2]: stage 1, exposed and necrotic bone or a fistula that probes to bone in patients who are asymptomatic and have no evidence of infection; stage 2, exposed and necrotic bone or a fistula that probes to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage; and stage 3, exposed and necrotic bone or a fistula that probes to bone extending beyond the region of alveolar bone in patients with pain, infection,

and one or more of the following—pathologic fracture, extraoral fistula, oroantral or oronasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor.

SURGICAL PROCEDURES

Patients were treated conservatively before surgery with antibiotics (1 g of third-generation cephalosporin given intravenously twice daily), analgesics, daily irrigation with 0.12% chlorhexidine, and professional dental prophylaxis during the 1-week period before surgery. Surgical procedures were performed with local anesthesia with the patient under intravenous sedation or general anesthesia, depending on the extent of the lesion and the patient's general condition. Bony sequestra and granulation tissue were removed by surgical curettes until fresh bleeding from bone was confirmed (Fig 1). Rotary instruments were used to smoothen out all sharp bony margins, followed by thorough irrigation with antibiotic solution (2 g of third-generation cephalosporin in 1 L of saline solution) to minimize further bacterial contamination and to remove debris and foreign bodies.

Patients were randomly assigned to undergo either placement of L-PRF alone or placement of combined L-PRF and recombinant human BMP-2 (rhBMP-2) on the bony defect. For the preparation of L-PRF, 20 mL of peripheral blood was collected into two 10-mL tubes without anticoagulant and immediately centrifuged at 3,000 rpm for 10 minutes. Then L-PRF was acquired from the tube after the red corpuscles and the acellular plasma at the bottom and top of the tube, respectively, were discarded (Fig 2). For the preparation of rhBMP-2, a commercially available kit (Novosis; Daewoong Pharma, Seoul, Republic of Korea) containing 0.5 mL rhBMP-2 solution and hydroxyapatite was used. As an rhBMP-2 carrier, a collagen sponge (Ateroplug; Bioland, Seoul, Republic of Korea) was sectioned into thin round shapes, which were soaked in the rhBMP-2 solution (Fig 3), and the hydroxyapatite from the kit was discarded. In patients who were assigned to receive L-PRF and rhBMP-2 simultaneously, collagen sponge sections with rhBMP-2 were placed with direct contact to the bone surface, followed by L-PRF application (Fig 4). Primary closure of the mucoperiosteal flap was then achieved. In patients who were treated with only L-PRF, L-PRF was placed at the bone surface and primary closure of the mucoperiosteal flap was performed. All resected tissues were sent to the pathology department to confirm the existence of bacterial colonies and to obtain the definitive pathologic diagnosis.

For postoperative management, an antibacterial mouth rinse was used in all patients until complete healing was confirmed. Intravenous antibiotics were

FIGURE 2. Leukocyte-rich and platelet-rich fibrin was obtained by collecting blood in a tube without anticoagulant and performing immediate centrifugation.

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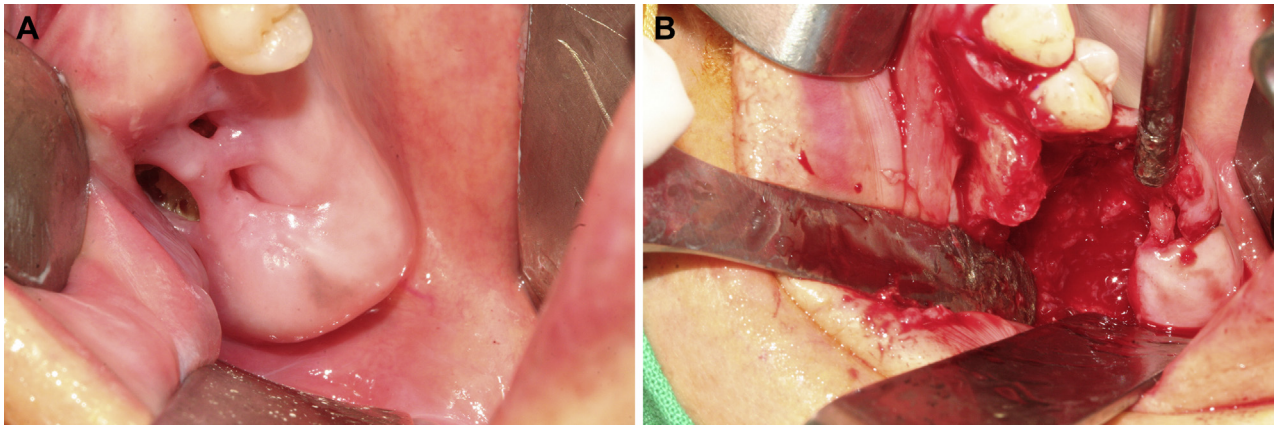

FIGURE 1. *A*, Lesion of medication-related osteonecrosis of the jaws preoperatively. *B*, Bony sequestra and granulation tissue were removed until fresh bleeding from bone was confirmed.

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FIGURE 3. Collagen sponge was sectioned into thin round shapes, which were soaked in the recombinant human bone morphogenetic protein 2 solution.

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continued for 1 week postoperatively, followed by oral antibiotics (third-generation cephalosporin) for 2 weeks. Unless mucosal swelling and erythema, purulent drainage, or any discomfort associated with the surgical site remained, antibiotics were discontinued at 3 weeks postoperatively.

ASSESSMENT OF TREATMENT RESULTS

After surgical treatment, patients were followed weekly for the first month and then monthly for 6 months. Surgical sites were clinically and radiographically evaluated at 4 and 16 weeks postoperatively for each patient. The presence of exposed bone, mucosal swelling and erythema, purulent drainage, intraoral or extraoral fistula, and/or any pain or discomfort associated with the surgical site was clinically evaluated. Radiographic examination was performed with panoramic views and computed tomography to assess for progression of bony destruction after the surgical procedure. Healing outcomes were classified as complete, delayed, or no resolution. *Complete resolution* was defined as full mucosal coverage with the absence of the aforementioned clinical or radiographic evidence of MRONJ at 4 weeks postoperatively. *Delayed resolution* was defined when clinical or radiographic evidence of MRONJ was present at 4 weeks but had resolved completely with full mucosal coverage by 16 weeks. *No resolution* was defined as persistence of clinical signs and symptoms or radiographic progression of MRONJ with exposed bone or with bone that could be probed through a fistula at 16 weeks postoperatively.

STATISTICAL ANALYSIS

Statistical analyses were performed with SPSS software (version 18.0; SPSS, Chicago, IL). Data were compared between groups by the t test and Mann-Whitney test for continuous variables and the χ^2 test and Fisher exact test for categorical variables. To analyze the association between the treatment method and the resolution of MRONJ, the odds ratio of disease resolution was estimated by use of ordinal logistic regression analysis with adjustment for patient-specific variables. All values were considered statistically significant at $P < .05$.

Results

The study sample was composed of 55 MRONJ patients. Of the 55 patients, 25 were treated with a single application of L-PRF (PRF group) and 30 were treated with simultaneous application of L-PRF and rhBMP-2 (PRF-plus-BMP group). The baseline characteristics in both groups are shown in Table 1. Over 85% of patients in this study received antiresorptive therapy for osteoporosis and only 7 patients (12.7%) for bony

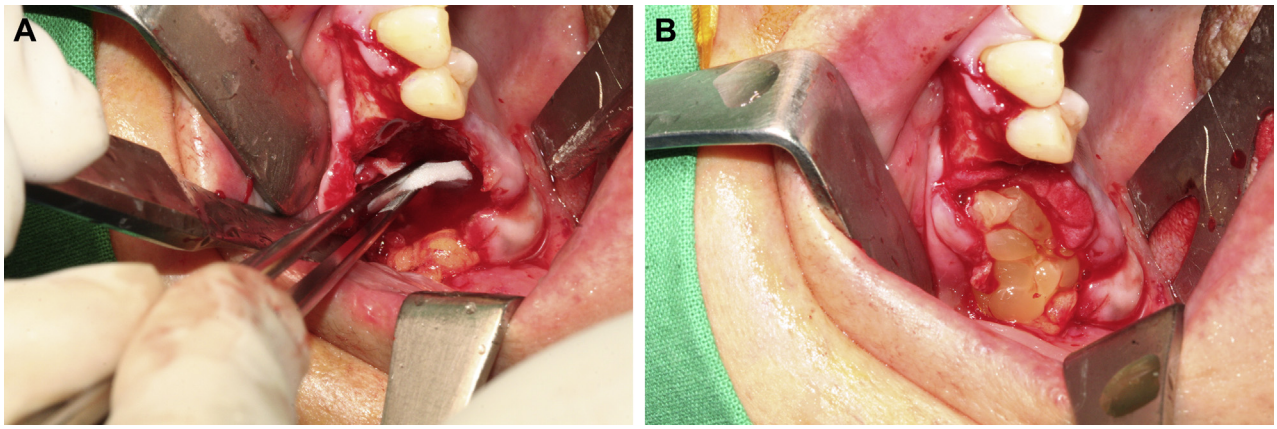

FIGURE 4. Collagen sponge sections with recombinant human bone morphogenetic protein 2 were inserted with direct contact to the bone surface (*A*), followed by the application of leukocyte-rich and platelet-rich fibrin (*B*).

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Table 1. CHARACTERISTICS OF STUDY POPULATION

	L-PRF (n = 25)	L-PRF Plus BMP-2 (n = 30)	*P* Value
Age, mean (range), yr	75.24 (59-97)	75.2 (60-85)	.983
Observation period, mean (range), mo	10.12 (6-26)	10.43 (6-31)	.607
Gender, n			
Female	22 (88.0%)	29 (96.7%)	.320
Male	3 (12.0%)	1 (3.3%)	
Reason for antiresorptive therapy, n			
Osteoporosis	22 (88.0%)	26 (86.7%)	>.99
Bone metastasis	3 (12.0%)	4 (13.3%)	
Route of antiresorptive agent administration, n			
Orally	3 (12.0%)	4 (13.3%)	>.99
Intravenous	22 (88.0%)	26 (86.7%)	
Type of antiresorptive agents, n			
Alendronate	15 (60.0%)	15 (50.0%)	.434
Risedronate	2 (8.0%)	5 (16.7%)	
Pamidronate	0 (0%)	3 (10.0%)	
Zoledronate	0 (0%)	1 (3.3%)	
Ibandronate	3 (12.0%)	3 (10.0%)	
Multiple	5 (20.0%)	3 (10.0%)	
Duration of antiresorptive therapy, mean (range), mo	48.32 (24-120)	59.73 (12-180)	.670
Dental etiologic risk factors, n			
Tooth extraction	15 (60%)	20 (66.7%)	.789
Implantation	2 (8.0%)	4 (13.3%)	
Ill-fitting prosthesis	3 (12.0%)	2 (6.7%)	
Spontaneous occurrence	5 (20.0%)	4 (13.3%)	
Other risk factors, n			
Steroid taking	5 (20%)	5 (16.75)	>.99
Diabetes*	7 (28.0%)	10 (33.3%)	.773
AAOMS stage, n			
I	2 (8.0%)	6 (20.0%)	.328
II	22 (88.0%)	21 (70.0%)	
III	1 (4.0%)	3 (10.0%)	
Site, n			
Maxilla	10 (40%)	6 (20%)	.153
Mandible	15 (60%)	22 (73.3%)	
Both	0 (0%)	2 (6.7%)	
sCTX, n			
≥150 pg/mL	17 (68.0%)	16 (53.3%)	.269
<150 pg/mL	8 (32.0%)	14 (46.7%)	
Existence of bacterial colony, n	5 (20.0%)	12 (40.0%)	.110

Abbreviations: AAOMS, American Association of Oral and Maxillofacial Surgeons; BMP-2, bone morphogenetic protein 2; L-PRF, leukocyte-rich and platelet-rich fibrin; sCTX, serum concentration of C-terminal cross-linked telopeptide of type I collagen.

* Fasting glucose concentration in serum of 6.99 mmol/L or more, taking drugs for diabetes, or taking insulin.

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metastatic disease. Alendronate was used in over 50% of the patients in both groups, and only 1 patient received zoledronate. The patients were well matched between the 2 groups regarding age, gender, observation period, reason for antiresorptive therapy, route of administration, type of antiresorptive agents, duration of antiresorptive therapy, dental etiologic factors, and other risk factors for MRONJ development. In addition, the distribution of AAOMS stages, site of MRONJ, sCTX level, and existence of bacterial colonies were not significantly different between the 2 groups.

The treatment results of the 2 groups are displayed in Table 2. At 4 weeks postoperatively, 18 patients in the PRF-plus-BMP group (60.0%) showed complete resolution of lesions whereas 9 patients in the PRF

Table 2. TREATMENT RESULTS OF BOTH GROUPS

	L-PRF (n = 25)	L-PRF Plus BMP-2 (n = 30)
Complete resolution, n	9 (36.0%)	18 (60.0%)
Delayed resolution, n	13 (52.0%)	11 (36.7%)
No resolution, n	3 (12.0%)	1 (3.3%)

Abbreviations: BMP-2, bone morphogenetic protein 2; L-PRF, leukocyte-rich and platelet-rich fibrin.

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group (36.0%) showed complete resolution. Twelve patients in the PRF-plus-BMP group and 16 patients in the PRF group exhibited bone exposure or symptoms at the 4-week postoperative follow-up. At 16 weeks postoperatively, 11 patients in the PRF-plus-BMP group (36.7%) and 13 patients in the PRF group (52.0%) showed complete resolution. There was a significant association between the resolution of MRONJ and the treatment method (Table 3). MRONJ healing was significantly improved in the PRF-plus-BMP group compared with the PRF group (odds ratio, 4.172; 95% confidence interval, 1.165 to 14.944; P = .028), indicating that the additional use of BMP-2 significantly improved MRONJ healing.

The association between the resolution of MRONJ and other clinical factors also was evaluated by logistic regression analysis (Table 3). The existence of bacterial colonies in the biopsy specimens was a significant factor negatively affecting the resolution of disease. The odds ratio for absence of bacterial colony relative to existence of bacterial colony was 5.812 (95% confidence interval, 1.378 to 24.510; P = .017), denoting that absence of active infection in the surgical site led to better healing compared with none. There was no significant association between the resolution of MRONJ and the following clinical factors: gender, age, reason for antiresorptive therapy, route of administration, duration of antiresorptive therapy, AAOMS stage, sCTX level, use of steroids, and medical history of diabetes.

Discussion

This study aimed to investigate the effect of the addition of BMP-2 to L-PRF on the treatment of MRONJ. L-PRF is known to be an effective adjunct in treating MRONJ,[15] although because of the absence of BMPs within L-PRF, there is doubt regarding whether it is an effective treatment for MRONJ, which is primarily thought to be an osseous disease. Because oversuppression of bone remodeling is thought to be one of the main pathogeneses of MRONJ, BMP-2 has a potential role of enhancing bone remodeling on the remodeling-suppressed bone of MRONJ. Thus we hypothesized that the addition of BMP-2 to L-PRF stimulates not only soft tissue healing but also osseous remodeling, contributing to the successful treatment of MRONJ. This study compared the healing outcome of combined use of BMP-2 and L-PRF with single use of L-PRF in the surgical treatment of MRONJ. The association between MRONJ resolution and patient-specific factors that may influence the treatment outcome of MRONJ also was adjusted and analyzed.

This study showed a significant association between resolution of MRONJ and combined therapy of L-PRF and BMP-2 compared with single L-PRF therapy. Differences between the 2 groups were exhibited especially in the healing periods. Patients in the PRF group showed more delayed healing patterns than those in the PRF-plus-BMP group. Because the AAOMS guideline suggested prioritizing continued antiresorptive therapy,[2] patients may benefit from this combined therapy because early healing of lesions can allow continuous antiresorptive therapy. The presence of a bacterial colony, denoting active infection of the MRONJ lesion, was a significant negative factor affecting resolution after the surgical procedure regardless of treatment regimen. Because all patients received intravenous antibiotics during the 1-week period before surgery and 3 weeks after surgery, these results show that antibiotic therapy does not improve outcomes when active infection is present.

L-PRF, first introduced by Choukroun et al[15], is prepared by collecting blood in a tube without anticoagulant and performing immediate centrifugation.[25] Compared with platelet-rich plasma, L-PRF is characterized as having a physiologically more favorable fibrin architecture obtained by a slow and natural coagulation process.[26] During polymerization, platelets, leukocytes, cytokines, and circulating stem cells are incorporated into the fibrin network.[27] The stable fibrin matrix of L-PRF does not dissolve quickly and allows progressive release of cytokines and growth factors of platelets.[28] In addition, the leukocyte within L-PRF acts as an anti-infectious agent and has a role in immune regulation and production of a large amount of vascular endothelial growth factor.[25] Thus, L-PRF accelerates epithelial wound healing, promotes tissue vascularization, and enhances regeneration of soft tissues. Nevertheless, considering the absence of BMP, the direct therapeutic effect of L-PRF on MRONJ healing appears to be unclear because MRONJ has been primarily thought to be an osseous disease.

The osteoinductive capacity of BMP-2, stimulating osteoblast differentiation and proliferation, has been shown in numerous studies.[24] However, BMP-2 also

Table 3. ASSOCIATION BETWEEN CLINICAL FACTORS AND RESOLUTION OF MRONJ AFTER TREATMENT

Variable	Odds Ratio	95% CI	*P* Value
BMP-2 use			
Yes (L-PRF plus BMP-2)	4.172	1.165-14.944	.028*
No (L-PRF)	1 (reference)		
Age			
≤75 yr†	1.108	0.336-3.659	.866
>76 yr	1 (reference)		
Gender			
Male	0.209	0.015-2.892	.243
Female	1 (reference)		
Reason for antiresorptive therapy			
Osteoporosis	0.535	0.079-3.634	.522
Bone metastasis	1 (reference)		
Route of antiresorptive agent administration			
Orally	0.866	0.117-6.410	.888
Intravenous	1 (reference)		
Duration of antiresorptive therapy			
≤40 mo‡	1.203	0.348-4.158	.770
>41 mo	1 (reference)		
AAOMS stage			
I	19.056	0.637-569.854	.089
II	2.314	0.192-27.865	.509
III	1 (reference)		
sCTX			
≥150 pg/mL	1.942	0.509-7.401	.331
<150 pg/mL	1 (reference)		
Existence of bacterial colony			
No	5.812	1.378-24.510	.017*
Yes	1 (reference)		
Steroid administration			
No	3.573	0.605-21.100	.160
Yes	1 (reference)		
Diabetes			
No	0.677	0.155-2.967	.605
Yes	1 (reference)		

Abbreviations: AAOMS, American Association of Oral and Maxillofacial Surgeons; BMP-2, bone morphogenetic protein 2; CI, confidence interval; L-PRF, leukocyte-rich and platelet-rich fibrin; MRONJ, medication-related osteonecrosis of jaws; sCTX, serum concentration of C-terminal cross-linked telopeptide of type I collagen.

* Statistically significant by ordinal logistic regression analysis.

† The median age of the patients was 75 years.

‡ The median duration of antiresorptive agent administration was 40 months.

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exhibits biphasic function of bone resorption by osteoclast activation, which is regarded as a regulatory mechanism of bone mass,[29] and as reported by several in vitro studies, BMP-2 directly stimulates osteoclast differentiation.[30,31] Because the main pharmacologic effect of antiresorptive drugs is inhibition of osteoclasts, MRONJ is understood as a disease mainly associated with the oversuppression of bone remodeling. In an animal study, insertion of BMP-2 into the tooth sockets of dogs (previously exposed to zoledronic acid) was shown to counteract the negative effects of zoledronic acid on bone healing and remodeling.[23] In addition, a clinical trial supported the feasibility of BMP-2 in the treatment of MRONJ.[22] Through biphasic function, BMP-2 seems to have a reversal effect on remodeling-suppressed bone of MRONJ, thus enhancing bone remodeling. As fibrin is a recognized support matrix for BMP,[32] the stable fibrin of L-PRF is expected to have played a role as a support matrix for BMP-2 in our study. BMP-2 enmeshed in the L-PRF matrix may be progressively released, thus affecting the MRONJ lesion directly. This implies that BMP-2 within the fibrin matrix, such as L-PRF, is expected to stimulate both soft tissue healing and bone remodeling, thus contributing to the successful treatment of MRONJ.[33]

According to the literature, the most common clinical findings in patients with MRONJ are the classic signs of infection, and bacterial colonization is present in over 80% of patients with MRONJ.[34] *Actinomyces* has been reported to be the most common microorganism associated with MRONJ, and it has been shown that lesions infected by *Actinomyces* require longer treatment because of the considerably prolonged duration of the disease.[35] In our study active infection of the MRONJ lesion was a significant negative factor for the resolution of MRONJ. Even though antibiotic therapy continued, active infection impedes healing regardless of surgery with an adjunct. Conservative management with antibiotics is definitely necessary to control infection in MRONJ patients; however, improved outcomes are seen when MRONJ-associated microorganisms are considered in antibiotic selection coupled with supplementary treatment to control active infection.

There is no standard of management for MRONJ, which mainly stems from the unclear pathophysiological mechanism of the disease. The treatment goal is preservation of patients' quality of life through pain control, infection management, and prevention of lesion progression.[2] Despite the opinion that conservative nonsurgical treatment, such as antibiotics and disinfectant mouth rinse, is the preferential method of MRONJ treatment, there seems to be a trend of surgical treatment, which shows predictable healing outcomes with a success rate of 73 to 100% after surgical resection.[36] Recently, a prospective study showed that surgical management of MRONJ enhanced mucosa healing and positively influenced the clinical outcome compared with conservative treatment.[37] A systematic review reported that the average healing rates for surgical management were 84% for extensive surgery, 85% for extensive laser-assisted surgery, and 75% for conservative surgery.[38] However, the outcomes of nonsurgical management showed low healing rates, with 36% for antibiotic therapy alone and 30 to 52% for antibiotic therapy in combination with low-level laser therapy or hyperbaric oxygen therapy.[38] In this study the success rate of surgical treatment, involving removal of necrotic bone until fresh bleeding from bone was confirmed, was 96.7% for L-PRF in combination with rhBMP-2 and 88% for L-PRF alone.

This study has limitations of a small sample size and absence of a control group because of the rarity of MRONJ. In addition, there was no group treated with single use of BMP-2 to compare healing outcomes. Properly designed, randomized, prospective trials with larger sample sizes are needed to confirm the possible additive effect of combined therapy using L-PRF and BMP-2.

In conclusion, simultaneous application of L-PRF and BMP-2 effectively contributes to the successful treatment outcome of MRONJ. The combined treatment leads to the early resolution of MRONJ; thus patients who need to continue antiresorptive therapy may benefit from the combined regimen.

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