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Use of Recombinant Bone Morphogenetic Protein 2 in Free Flap Reconstruction for Osteonecrosis of the Mandible

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Abstract

Purpose: Osteoradionecrosis of the mandible is a debilitating consequence of radiation therapy for head-and-neck malignancy. It can result in pain, bone exposure, fistula formation, and pathologic fracture. Recombinant human bone morphogenetic protein 2 (rhBMP-2) has shown promise in reconstruction of bone defects. The purpose of this study is to determine whether the addition of rhBMP-2 at the union of vascularized bone and native bone improves surgical outcomes in patients with osteonecrosis of the mandible.

Materials and Methods: This study was a retrospective analysis of patients who were treated between 2006 and 2010 for osteonecrosis of the mandible. Patients requiring definitive reconstruction after failure of a course of conservative management were included. Patients were divided into 2 cohorts depending on whether rhBMP-2 was used during the reconstruction. The primary outcome measure was defined as stable mandibular union.

Results: Seventeen patients were included. The development of malunion was similar in both groups (13% for rhBMP-2 group vs 11% for non-rhBMP-2 group). Infectious complications were similar between the groups (25% in rhBMP-2 group vs 56% in non-rhBMP-2 group, $P = .33$). The

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The use of recombinant bone morphogenetic protein 2 (Infuse Bone Graft; Medtronic, Minneapolis, MN) was off label. We received no funding from Medtronic, nor do we have any other relationship with Medtronic. The authors have nothing else to disclose.

rates of hardware removal were similar for the 2 groups (33% in non-rhBMP-2 group vs 25% in rhBMP-2 group, $P = .10$). No cancer recurrences were observed in patients receiving rhBMP-2.

Conclusions: The use of rhBMP-2 is safe in free flap reconstruction of the mandible, but its ability to significantly improve patient outcomes, as measured by rates of malunion, reoperation, or infection, is still unknown.

Osteoradionecrosis (ORN) of the mandible is one of the most debilitating consequences of radiation therapy for head-and-neck malignancy. The triad of hypoxia, hypocellularity, and hypovascularity comprises the histologic changes associated with ORN.^{1,2} These histopathologic changes can manifest as pain, bone exposure, fistula, and pathologic fracture. These manifestations can significantly impact speech, diet, and quality of life. Although the actual number of patients affected is unclear, prevalence estimates range from 6% to 7% in patients who have undergone some form of radiotherapy for head-and-neck cancer,³ and some authors estimate that as many as 50% of patients who have symptoms associated with ORN will require surgery.^{4,5}

Conservative management of ORN usually involves antibiotics and hyperbaric oxygen therapy, often in combination with local debridement.^{6,7} If conservative measures fail to resolve the disease process,⁸ then definitive surgical intervention is required. Treatment of refractory ORN involves complete resection of the diseased bone followed by efforts to re-establish mandibular continuity. Reconstruction of the mandible can be undertaken with titanium reconstruction plates or with vascularized bone grafting.⁹⁻¹¹

Several recent studies have shown that free flap reconstruction is a viable option for reconstruction of the mandible after resection for ORN, with disease resolution rates reported between 86% and 100%. In addition, it has been shown that free flap reconstruction can lead to improved oral function and quality of life.¹² However, in this setting, free flap procedures are associated with higher failure rates and malunion, and as a result, every attempt is made to improve surgical outcomes.¹³⁻¹⁶

Recombinant bone morphogenetic protein 2 (rhBMP-2) has been shown to induce osteoblastic differentiation and promote bone formation by endochondral ossification.^{17,18} It has been used clinically in spinal fusion procedures because of its ability to produce vertebral fusion and stability¹⁹ and has been found to be effective in reconstructing alveolar clefts^{20,21} and maxillary sinus defects.²² In addition, there is a case study suggesting that rhBMP-2 alone can be used to reconstruct segmental mandibular defects in the absence of previous radiotherapy.²³ It has also been shown to improve surgical outcomes when used in repair of complex long bone fractures.²⁴ Importantly, animal studies have shown that new bone formation could be induced in an irradiated tissue bed with the use of rhBMP-2.^{25,26} As a result, given that ORN defects are often associated with poor wound healing and prevention of bony unionization, we retrospectively reviewed our use of rhBMP-2 when placed at the union of vascularized bone and native mandible in patients undergoing reconstruction of the mandible for ORN. The aim of this study was to determine whether the use of rhBMP-2 improved outcomes and decreased complication rates in patients undergoing free flap reconstruction of the mandible for ORN.

Materials and Methods

PATIENTS

After institutional review board approval, a retrospective review was conducted of patients who received free flap reconstruction at the University of Alabama at Birmingham. Seventeen patients who were treated with mandibular resection and osseous free flap reconstruction for refractory osteonecrosis of the mandible from 2006 to 2010 were

included. Exclusion criteria included patients who were treated before rhBMP-2 (Infuse Bone Graft; Medtronic, Minneapolis, MN) was available or were within 1 year of surgery and, therefore, were not candidates for rhBMP-2 placement, to avoid potential stimulation of residual cancer cells.

Clinical parameters including age, gender, previous cancer site and histology, previous cancer therapy, time from last radiation to reconstruction, previous mandibulotomy, medical comorbidities, and follow-up time were also evaluated. Operative details including indication for surgery, site and size of mandibular defect, and type of free flap used were included as well. In addition, outcomes data including flap complications (infection, hardware exposure, failure), reoperation, mandibular union, persistent pain, oral incompetence, and diet were evaluated. Mandibular union was defined by clinical examination (pain-free, immobile mandible) and radiographic evidence (panoramic radiography or plain film imaging) of stability at 6 months to 1 year.

Patients who underwent free flap reconstruction of the mandible with the use of rhBMP-2 were compared with those who did not receive rhBMP-2. If the patient received rhBMP-2, it was prepared according to the manufacturer's instructions and placed between the osteotomy sites of the native mandible and the vascularized bone graft. This was an off-label use of rhBMP-2. There were no guides or models used, and to ensure that there were no osteotomy gaps, good bone contact was established at each site. A 2.0-mm reconstruction locking plate was used for all cases, and there was no variation based on flap type or buttressing of the osteotomies.

STATISTICAL EVALUATION

Statistical calculations were conducted with GraphPad software (GraphPad, San Diego, CA). Categorical data were compared by use of the Fisher exact test, and continuous data were compared by use of an unpaired *t* test and analysis of variance, where appropriate. All statistical tests were 2 tailed. $P < .05$ was considered statistically significant.

Results

A total of 17 patients were included in the study. All patients were referred for definitive reconstruction of the mandible and had previous conservative management, which varied considerably among patients but was limited to hyperbaric oxygen therapy (53%, $n = 9$), local wound care (53%, $n = 9$), intravenous antibiotics (35%, $n = 6$), or some combination thereof.

We identified 9 patients (53%) who did not receive rhBMP-2 at the time of reconstruction and 8 patients (47%) who did receive rhBMP-2. Most of the patients undergoing reconstruction without the use of rhBMP-2 were men, but this difference was not statistically significant ($P = .34$) (Table 1). There were no statistically significant differences in mean age ($P = .33$), mandibulotomy before radiation treatment ($P = .62$), or medical comorbidities ($P = .29$), which were defined as any medical condition for which the patient was receiving treatment at the time reconstruction was undertaken (Table 1). The mean duration from the last radiation therapy treatment was 67 months in the non-rhBMP-2 group and 37 months in the rhBMP-2 group ($P = .18$) (Fig 1). There were 2 patients in the rhBMP-2 group who did not have a history of head-and-neck cancer and therefore had never received radiation therapy.

Most patients (88%, $n = 15$) had a history of head-and-neck squamous cell carcinoma. There was 1 patient in the rhBMP-2 group who was originally treated for ameloblastic fibrosarcoma and 1 patient in the non-rhBMP-2 group who was previously treated for

adenocarcinoma of the submandibular gland. There was a statistically significant difference between the treatment groups and the type of flap used for reconstruction ($P = .05$). Most patients in the non-rhBMP-2 group underwent reconstruction with an osteocutaneous fibula free flap ($n = 8$), whereas only 1 patient underwent reconstruction with an osteocutaneous radial forearm free flap. In the rhBMP-2 group, 3 patients underwent reconstruction with fibula free flaps and 5 underwent reconstruction with osteocutaneous radial forearm free flaps. The indications for reconstruction included orocutaneous fistula, pathologic fracture, persistent bone exposure, and persistent pain (Table 2).

When comparing complication occurrences between the 2 groups, we found no statistically significant differences in infection rates ($P = .35$), hardware exposure ($P = .10$), or need for additional surgery ($P = .62$) (Fig 2). Of note, there were no instances of carotid blowout or anastomotic leak. There was 1 flap failure in the non-rhBMP-2 group, and this required a pectoralis major myocutaneous flap as a salvage procedure.

When comparing the surgical outcomes (stable fusion rates, persistence of feeding tubes, and incidence of oral incompetence), we found that there were no statistically significant differences between the 2 groups ($P = .14$) (Fig 3). There was 1 occurrence of malunion in the rhBMP-2 group, and it was found at reoperation that the patient had a chronic hardware infection with nonunion between the native mandible and the vascularized bone graft. The rates of hardware removal were similar for the 2 groups (33% in non-rhBMP-2 group vs 25% in rhBMP-2 group, $P = .10$).

Of the 17 patients, 4 were excluded from the long-term outcomes analysis for lack of follow-up, 2 from the non-rhBMP-2 group and 2 from the rhBMP-2 group. The remaining patients had an overall median follow-up greater than 12 months. There was no evidence of disease recurrence in either group, suggesting that the use of rhBMP-2 is safe in this patient population. The recommended post-reconstruction follow-up for ORN patients is 12 to 18 months.

Discussion

We show in a case series of 17 patients treated with microvascular reconstruction for advanced-stage osteonecrosis that use of rhBMP-2 is safe, but its efficacy in preventing malunion could not be clearly established. ORN is associated with poor wound healing and failure of unionization between the mandible and grafted bone. This is associated with significant morbidity including orocutaneous fistula, pain, persistent bone exposure, speech difficulties, and malnutrition. Management is typically conservative, and little is known about how to improve outcomes. In a recent study of 73 patients, fewer than 10 received aggressive surgical management, and of those, only 2 received free tissue transfer.⁵ As in our study, this is partly because of the low incidence of ORN, limiting the sample size and making larger studies challenging. With the advent of rhBMP-2 and promising studies indicating that it increases bone fusion rates¹⁹ and induction of new bone formation in irradiated tissue beds,^{25,26} its potential ability to improve union rates between the mandible and grafted bone was investigated.

We found no significant differences between the baseline characteristics for the 2 groups, which included duration of ORN, previous conservative management, and method of reconstruction. There was a statistically significant difference in the type of free flap used for the reconstruction, with more fibula free flaps used in the non-rhBMP-2 groups ($P = .05$). However, there was no significant difference in the size of the defect between the 2 groups ($P = .62$), with a mean defect size of 6.3 cm in the non-rhBMP-2 group compared with 5.9 cm in the rhBMP-2 group. Previous publications have found the radial forearm free

flap to be comparable to the fibula free flap for functional outcomes and decreased morbidity.^{27,28} As a result, in this study the type of free flap used was a reflection of surgeon preference and not likely to have affected outcome.

In addition, there were no statistically significant differences in long-term functional outcomes, including feeding tube dependence and oral incompetence. The use of rhBMP-2 was found to be safe, with no cancer recurrences observed in patients receiving rhBMP-2. The malunion rates were not significantly different between groups, which is likely the result of the small sample size causing low power. In addition, the retrospective nature of our study inherently limits the amount and quality of data that are collected. Four patients had to be excluded from the long-term functional outcomes comparison for lack of follow-up (<3 months). However, these patients provided data on short-term complications and were included in the study for these analyses. Finally, because the administration of rhBMP-2 was not randomized, confounding variables are possible.

Whereas the use of rhBMP-2 in the spine has been associated with increased edema,^{29,30} we used a smaller quantity (1.05 mg) in this study and this is not likely to have stimulated an inflammatory response.^{29,31} In addition, edema is a known complication of the type of tissue manipulation involved in free flap reconstruction, and subsequently, there was no difference in the incidence and severity of swelling between the 2 groups. The overall complication rates for this investigation were 50% in the non-rhBMP-2 group and 50% in the rhBMP-2 group. In addition, the failure rates were 11% in the non-rhBMP-2 group and 13% in the rhBMP-2 group ($P > .99$). The complication rates in other reports of free flap reconstruction for ORN range from 20% to 60%, with failure rates ranging from 0% to 20%.^{13-16,32} These results would suggest that the use of rhBMP-2 is not associated with decreased complication rates.

In a previous study we reported that increased time from cessation of radiotherapy to diagnosis of ORN predicted increased risk of complications in free flap reconstruction for ORN.³³ In this study the mean time from last radiation therapy to reconstruction was significantly longer in the non-rhBMP-2 group (Fig 1); however, there was no statistically significant difference in the complication rates between the 2 groups. Had the duration from radiation therapy been the same for both groups, there may have been a more significant difference in the complication rates.

An important consideration in using rhBMP-2 in this patient population is safety. There is some concern that rhBMP-2 may promote growth of tumor cells. Although this is a valid concern, there are data to suggest that rhBMP-2 does not promote the growth of cancer cells in head-and-neck squamous cell cancer in vitro or in vivo.³⁴ In a large retrospective cohort study of patients who underwent spinal fusion with rhBMP-2, it was found that there was no increased risk of pancreatic cancer associated with the use of rhBMP-2.³⁵ These studies support the safety of rhBMP-2, but until the biology of rhBMP-2 has been fully elucidated, it is advisable to proceed with caution when using this modality in the setting of ORN. The surgeon should consider the patient's disease-free period before using rhBMP-2, and a preoperative biopsy should be performed to confirm that there is no cancer recurrence. In this study a disease-free period of at least 6 months was used, and the majority of patients had been disease free for greater than 1 year at the time of rhBMP-2 placement.

An additional factor to consider is the significant cost associated with the use of rhBMP-2. Several authors have conducted health economic analyses associated with the use of rhBMP-2 in clinical areas where benefit associated with its use has been shown. They found that the high upfront cost of the compound is mitigated by such factors as decreased hospital

stay and time away from work.^{36,37} Until significant benefit can be shown in free flap reconstruction, the cost of rhBMP-2 remains an important consideration.

The use of rhBMP-2 in the setting of osteocutaneous free flap reconstruction for ORN is feasible and safe. Although there were trends suggesting that the use of rhBMP-2 is associated with improved outcomes and a reduction in complication rates, the power was insufficient to draw statistically meaningful conclusions. Therefore further investigations are warranted to clarify whether the use of rhBMP-2 provides added benefits over the standard of care and if the cost is justified.

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FIGURE 1.

Duration from radiation therapy to reconstruction for ORN. The mean time from the last radiation treatment to reconstruction was 67 months for the non-rhBMP-2 group compared with 37 months for the rhBMP-2 group ($P = .18$ by 2-sided t test).

FIGURE 2.

Surgical complications. There were no statistically significant differences in infection rates ($P = .35$), hardware exposure ($P = .10$), or need for additional surgery ($P = .62$) between the non-rhBMP-2 and rhBMP-2 groups.

FIGURE 3.

Surgical outcomes. The main surgical outcomes evaluated were fusion rates, persistent feeding tube use, and incidence of oral incompetence. There were no statistically significant differences for any of the surgical outcomes between the 2 groups ($P = .14$).

Table 1**BASELINE PATIENT CHARACTERISTICS**

	Non-rhBMP-2 Group (n = 9)	rhBMP-2 Group (n = 8)
Mean age (yrs)	59	52
Male gender [No. (%)]	7 (78)	4 (50)
Medical comorbidities* [No. (%)]	8 (89)	5 (63)
Previous cancer site [No. (%)]		
OC	3 (33)	7 (88)
OP	5 (56)	1 (12)
Other [†]	1 (11)	0 (0)

Abbreviations: OC, oral cavity; OP, oropharynx.

* Disease processes requiring treatment at time of operation.

[†] Includes bisphosphonate-related osteonecrosis in rh-BMP-2 group and adenocarcinoma of submandibular gland in non-rhBMP-2 group.

Table 2**SURGICAL INDICATORS**

	Non-rhBMP-2 Group (n = 9) [No. (%)]	rhBMP-2 Group (n = 8) [No. (%)]
Orocutaneous fistula	2 (22)	3 (38)
Pathologic fracture	3 (33)	4 (50)
Persistent bone exposure	2 (22)	1 (12)
Pain	2 (22)	1 (12)