Osteonecrosis of the Jaw after Implant Surgery in Patients Treated with Bisphosphonates – A Presentation of Six Consecutive Cases

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ABSTRACT

Background: Osteonecrosis of the jaws in patients treated with bisphosphonates is mostly associated with intravenous bisphosphonates while the incidence associated with oral bisphosphonates is not significant.

Purpose: The purpose of this paper is to describe a series of cases of jaw osteonecrosis that may be associated with dental implant placement in patients who had taken nitrogen containing bisphosphonates via oral and/or intravenous route.

Patients: Six female patients were treated for osteonecrosis of the jaw after implant placement. An average age was 71.8 ± 6.5 years old and they had a history of bisphosphonate use. Two patients suffered from cancer and the other patients had osteoporosis. Two osteoporosis patients had taken only oral bisphosphonate and the other patients received intravenous bisphosphonates.

Results: Resection of necrotized bone, implant removal, and primary closure were performed in five patients and four patients showed uneventful healing. One patient presented recurrence at the maxilla and underwent further extraction and resection. One patient presented with an exposure of the bone after implant placement was treated with an advanced flap closure, and the implants were preserved.

Conclusion: Unusual jaw necrosis after dental implant surgery might be related with oral and/or intravenous bisphosphonates. Wide resection of necrotic bone, collagen graft, and primary closure are key factors for successful healing.

KEY WORDS: bisphosphonate, breast cancer, dental implant, jaw necrosis, multiple myeloma, osteoporosis

INTRODUCTION

Osteonecrosis of the jaw (ONJ) in patients treated with bisphosphonates was first described in 2003 with a series of case reports by Marx and Migliorati.^{1,2} The highest incidence of ONJ is attributed to intravenous (iv) dosages with an incidence of 0.7 to 12%, while oral

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nitrogen-containing bisphosphonates (N-BPs) were not found to be statistically significant with an incidence of 0.7 per one hundred thousand person-years of exposure.³ According to the systemic review about bisphosphonates and dental implant surgery, the intake of oral bisphosphonates did not influence short-term (1–4 years) implant survival rates.⁴ However, Mavrokokki and colleages⁵ found the incidence of ONJ to be 0.01 to 0.04% in 2007 and Sedghizadeh and colleagues showed up to a 4% incidence in 2009.⁶ Because of limited data about ONJ by oral N-BPs, there might be serious underreporting or unreported patients that are way higher than reported by pharmaceutical company.

Lazarovici and colleagues discovered that patients receiving N-BPs with greater potency such as iv formula developed ONJ in a shorter period of time.⁷ The suggested risk factors for ONJ are extraction, denture wearing, and bony prominences lined with thin mucosa such as tori, exostoses, and the mylohyoid ridge.

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However, ONJ could happen without any risk factor. ONJ is also found to be more common in the mandible in comparison with the maxilla by a 2:1 ratio.⁸

Although the incidence of ONJ seems to be rising, there is very limited evidence or documentation of ONJ after implant placement in patients taking oral N-BPs.^{9,10} Multiple studies have shown that bisphosphonate usage does not affect the survival of implants. Jeffcoat studied 25 age-matched bisphosphonate patients with 25 postmenopausal control subjects and found no significant difference in the implant survival after a 3-year assessment.¹¹ One hundred percent success rate was observed in the bisphosphonate group and no complications seen after 3 years. Bell and Bell showed the implant survival rate of bisphosphonate patients to be 95% while control group had a survival rate of 96.5%.¹² They had an average follow-up of 3 years, shortest being 4 months and the longest was 7 years and 5 months. None of the 42 patients treated showed signs of ONJ.¹² Grant and colleagues also placed four hundred sixtyeight implants in one hundred fifteen patients with a reported history of oral bisphosphonate therapy with a mean duration of 38 months. They did not find any evidence of ONJ.13 However, other authors have presented that implant should be avoided until more conclusive data are available.10

This case series aims to present viable cases of ONJ related to dental implant surgery as well as the management of such cases even though the literature does not support a positive correlation between oral N-BPs use and implant failure.

CASE SERIES

From 2009 to 2011, six patients were referred to the Department of Oral and Maxillofacial Surgery, College

of Medicine at the University of Ulsan, Asan Medical Center in Seoul, Korea. All patients were female and over 64 years old, with an average age of 71.8 ± 6.5 . All the lesions were associated with implant surgery and showed sequestra. Patients' demographic data, medical history, site of lesion, route of drug, name of drug, and duration of the drug use were listed in Table 1. General surgical principles were used for treating ONJ such as aseptic technique, complete removal of necrotic bone, grinding of the bone until fresh bone marrow exposure, primary suture, advanced flap with a releasing incision to cover exposed bone, and no bone grafting to prevent infection. Collagen was grafted to the defect sites and fibrin glue was added to prevent wound dehiscence and bone exposure. Resected tissues were examined under microscope after decalcification.

Case 1

A 64-year-old Korean woman was referred from local clinic. Her chief complaint was pain and swelling in the maxillary right molar after implant surgery. Her medical history consisted of back pain due to osteoporosis and she underwent total knee joint replacement in August 2010. All other medical history was noncontributory. The patient had a history of taking oral alendronate (Fosamax) for 4 years prior to implant surgery, and a single dose was taken postsurgery. Her dental history consisted of an extraction of the maxillary right molar 4 years ago. Sinus augmentation in addition to the simultaneous placement of three implants was completed in January 2011 (Figure 1). Gingival swelling and bleeding was observed 2 months after surgery in the area of #2 and #3 (Figure 2). The symptoms did not subside after a prescription for antibiotics and anti-inflammatory medications was taken for 4 weeks. Patient was then

TABLE 1 Case Summary												
No.	Age	Site	MH	iv or Oral	Name of Drug	Rx						
1	64	Rt Mx	Osteoporosis	Oral	Alendronate	4						
2	70	Rt Mn	Breast cancer	iv	Zolendronate	3						
3	79	Ant Mn	Osteoporosis	Oral	Alendronate	6						
4	75	Lt Mn	Osteoporosis	Both	Alendronate + zolendronate	4						
5	65	Rt Mn	Multiple myeloma	iv	Zolendronate	2						
6	78	Lt Mx	Osteoporosis	iv	Alendronate	1.5						

Ant = anterior; iv = intravenous; Lt = left; MH = medical history; Mn = mandible; Mx = maxilla; No = number of patient; Rt = right; Rx = duration of the taking medicine (year).



Figure 1 Panoramic radiograph showing radiolucency 4 months after implant and sinus lifting operation. Bone destruction was found in #2 distal area.

referred to the Asian Medical Center for further treatment. Under local anesthesia, the two posterior implants were removed and necrotic bone was resected on May 23, 2011 (Figure 3A). Collagen (Teruplug, Terumo, Japan) and fibrin glue (Tisseel, Baxter, Westlake Village, CA, USA) were applied, and primary closure was performed. Amoxicillin 500 mg and aceclofenac 100 mg was prescribed for 7 days. Healing was uneventful and no sign of recurrence was detected after a follow-up of 19 months (Figure 3B).

Case 2

A 70-year-old woman was referred from a local clinic in December 2009 with pain, bleeding, and swelling of the mandibular right quadrant after implant placement. Patient had a history of breast cancer that was treated with surgical resection 12 years ago. However, metastasis to the spine occurred in December 2008. All other medical history was noncontributory. She received iv zolendronate (Zomecta) once a month for 1 year from December 2008 to prevent further bone metastasis. Because of the no further cancer metastasis, three implants were placed in March 2009 at the local clinic. One month after implant placement, one implant was removed due to swelling, pain, and implant mobility. After the removal of the implant, the pain and bleeding did not resolve and worsened (Figure 4). #31 implant along with the necrotic bone surrounding the implant was resected (Figure 5). Sequestectomy and wide resection were completed (Figures 6 and 7). Collagen and fibrin glue were also applied and the wound was closed with primary closure. Healing was uneventful and no sign of recurrence was detected after a follow-up of 36 months (Figure 8).



Figure 2 Peri-implantitis around #2 and #3 and swelling of peri-implant tissues.



Figure 3 Necrotic bone and two implants were removed.



Figure 4 Panoramic radiograph showing bone necrosis after implant surgery.

Case 3

A 79-year-old female presented in July 2010 with bleeding and pain after implant placement in the mandibular anterior region. Patient had a history of osteoporosis diagnosed in a local orthopedic clinic and had taken oral N-BPs (Fosamax) for the past 6 years. She underwent total knee joint replacement of left side leg in 2009. She had mild hypertension, which was well controlled with medication. All other medical history was denied. Implant placement was completed in March 2010, and the onset of symptoms presented 2 months after surgery (Figure 9). #27 implant was removed after 2 months and necrotic bone was resected simultaneously (Figures 10– 12). Healing was uneventful after a follow-up of 2 years.

Case 4

A 75-year-old female was referred from a local clinic in January 2011. Her chief complaint was pain and



Figure 5 Necrotic bone and peri-implant infection around #31.

bleeding after implant placement. She had a history of osteoporosis treated with 4 years of alendronate and iv ibandronate on three occasions. All other medical history was noncontributory. Two implants were placed in the mandibular left quadrant in October 2010 and became symptomatic 2 months later. The two implants were removed and #19 was extracted at a local clinic in December 2010 (Figure 13). Symptoms were aggravated after the removal of the implants, and bloody exudates and gingival swelling were observed. After referral to our clinic, sequestrectomy and saucerization of the left mandible were performed, and healing was uneventful after a follow-up of 1 year and 6 months (Figures 14 and 15).

Case 5

A 65-year-old female underwent implant surgery at Department of Periodontics, Asan Medical Center.



Figure 6 Necrotic bone and implant were removed and saucerization was performed.



Figure 7 Removed implant and necrotic bone.



Figure 10 Implant was displaced and bone necrosis was observed.



Figure 8 Intraoral photograph showing good healing state in the right mandible (postoperative 2 years and 9 months).

Denudation of bone in conjunction with pain and buccal swelling was observed after implant placement. Patient had suffered from multiple myeloma for 5 years and had a history of iv zolendronate every 4 weeks for 2 years. She was free of monoclonal gammopathy after chemotherapy. All other medical history was noncontributory. After consult with oncologist, two implants were placed in the mandibular right posterior region in June 2010. Progressive soft tissue dehiscence occurred immediately after implant surgery. Chlorhexidine irrigation and plaque control did not improve the soft tissue condition (Figure 16). On August 2010, the healing abutment was removed and the dehiscence was treated, and a submucosal flap suture was placed to achieve primary closure under local anesthesia (Figure 17). Symptoms subsided after primary healing



Figure 9 Implant installation to anterior mandible.



Figure 11 Removal of the implant and saucerization of necrotic bone.



Figure 14 Exposure of the necrotic bone.



Figure 12 Removed necrotic bone and implant.

(Figure 18). The implant was then uncovered and residual sequestrum was removed in April 2011. A second surgery was required to remove necrotic crestal bone resulting in exposure of three to four implant threads. However, implant mobility was not detected. Patient refused to remove the implant due to the lack of pain. The final restoration was delivered in October 2011 and no more soft tissue dehiscence was observed during follow-up periods of 14 months (Figure 19).

Case 6

A 78-year-old female was referred from local clinic for treatment of peri-implantitis (Figure 20). Her chief complaint was discomfort in the maxillary left region after implant placement. She had a history of osteoporosis and took oral bisphosphonate (alendronate) for 1.5 years. She denied other systemic disease. Dental



Figure 13 Osteonecrosis of the posterior mandible after implant installation. Implants were removed 2 months after surgery.



Figure 15 Removed bone from the left mandible.



Figure 17 Submucosal flap for primary closure after removal of the healing abutment.

implants were placed in the maxillary left quadrant in June 2009 (Figure 21). Recurrent gingival swelling presented 1 year after implant placement. Patient was treated with periodic scaling and periodontal care but symptoms did not subside. After her referral to Asan Medical Center, the three implants were removed and saucerization was completed in January 2011 (Figure 22). Healing was uneventful for 5 months until recurrent swelling and pain was observed on tooth #11 (Figure 23). Extraction of the canine was then completed and further resection was performed in July 2011 (Figure 24). No further inflammation or swelling was detected after the second surgery. Histopathologic examination showed inflammatory cell infiltration around sequestrum (Figure 25).

RESULTS

ONJ occurred in the maxilla in two patients and in the mandible in four patients. Four patients suffered from osteoporosis and two patients had cancer (metastatic breast cancer and multiple myeloma). All patients were surgically treated and oral antibiotic was prescribed. An average follow-up period was 26.0 ± 7.8 months after first surgery. The quality of bone prior to implant surgery, duration of edentulism, dental work prior to implant placement, one- or two-stage operation, type of implants, and qualification of the implant surgeon were listed in Table 2. Resection of necrotized bone, implant removal, collagen graft, and primary closure were performed in five patients and four patients showed uneventful healing. One patient (No. 6) presented fistula



Figure 16 Denudation of the bone after implant installation.



Figure 18 Healed mucosa after primary closure.



Figure 19 Definitive restoration showing bone loss around crestal bone after 1.5 years.



Figure 22 Implant removal and saucerization of necrotic bone.



Figure 20 Gingival recession and peri-implantitis were observed.

and pus discharge after first surgery and underwent further extraction and resection. One patient presented with an exposure of the bone after implant placement was treated with an advanced flap closure, and the implants were preserved.

DISCUSSION

The clinical efficacy of N-BPs is well established and prescribed worldwide in patients with metastatic cancer, multiple myeloma, and osteoporosis. Implant surgery in patients taking oral N-BPs is not contraindicated in osteoporotic patients. Short-tem result of implant survival showed no higher risk in those who received N-BP therapy and the placement of an implant may be considered a safe procedure in patients taking oral N-BP for less than 5 years.⁴ Koka and colleagues interviewed 82 postmenopausal nonbisphosphonate users and 55 postmenopausal bisphosphonate users and reported that



Figure 21 Bone loss around implants in the left maxilla.



Figure 23 Recurrence of the jaw necrosis after first operation.

ONJ was not observed in any of the patients, and the survival rates of the implants placed were 98.2% in the nonbisphosphonate group and 99.2% in the bisphosphonate group.¹⁴ Although previous studies have shown little or insignificant association between oral bisphosphonate therapy and ONJ, cases of ONJ after implant therapy do exist.^{9,10,15,16}

Current opinion contraindicates implant surgery in patients who received iv N-BPs.¹⁷ However, many dentists perform implant surgery on patients who had received iv N-BPs. According to the American Association of Oral and Maxillofacial Surgeons' position paper in 2009, it was recommended for patients to suspend N-BPs therapy 3 months prior and 3 months postoral surgery if the patient had been using it for over 3 years.¹⁸ Even though dental implant surgery is not contraindi-



Figure 24 Further extraction of the left maxillary canine and resection of the necrotic bone.



Figure 25 Photomicrograph showing inflammatory cell infiltration around sequestrum (hematoxylin and eosin staining, original magnification ×200).

cated in patients taking oral N-BPs, oral minor surgical procedures are risk factors for ONJ, so we must be prudent to place implant in those patients. In our case series, two patients taking oral N-BPs developed ONJ. One hypothesis regarding implants as causing factor for ONJ is that the surgical trauma during implant surgery could have stimulated the postoperative accumulation of the drug in the implant sites who takes bisphosphonate continuously after operation.⁹

Dental implant failure could be influenced by systemic or local factors. Among local factors, poor bone quality and quantity, inexperienced surgical technique, thermal damage, and bacterial infection could be major factors for implant failure.19 However, most of the implant failure by thermal damage and bacterial infection typically showed marginal bone loss or bone loss around dental implant.²⁰ In our case series, five patients showed bone destruction around dental implant and formed sequestra that are commonly observed in osteomyelitis of jawbone. In histologic examination, inflammatory cell was infiltrated around sequestrum; however, bacterial collection was not observed. It could be speculated in our case series that other factors are related with implant failure and bisphosphonates could be one of the causative factors. Implant surgery was performed by four specialists and two general practitioners. Surgical technique might not be the leading causative factors for implant failure in our study because of the experiences of the surgeons.

The treatment objectives for patients with ONJ are to eliminate pain, control infection, and minimize

TABLE 2 Bone Quality, Edentulous Periods, Dental Work before Implant Placement, Type of Implant, Implant Surgeon, and Follow-Up Months after Surgery												
No.	Age	BQ	EP(M)	DW	IS	Type of Implant	Implant Surgeon	FU(M)				
1	64	D4	48	No	1	One plant	Periodontist	19				
2	70	D2	6	Bridge	2	Neoplant	OMS surgeon	36				
3	79	D2	48	Bridge	2	Osstem USI	GP	24				
4	75	D3	6	No	2	3i	Prosthodontist	24				
5	65	D2	6	No	1	Osstem USII	Periodontist	18				
6	78	D3	4	No	1	Restore	GP	35				

BQ = bone quality; DW = dental work before implant surgery; EP = edentulous periods after extraction; FU = follow-up; GP = general practitioners; IS = implant surgery; M = months; OMS = oral and maxillofacial surgeon; 1 = one-stage surgery; 2 = two-stage surgery.

progression of bone necrosis and soft tissue dehiscence. The general principles of treating ONJ are complete resection of the necrotic bone, grinding of bone until fresh blood coming from the native bone, primary closure, and antibiotic therapy. If necrotic bone is left after resection, symptoms of pain and purulent discharge may recur. Lazarovici and colleagues treated 78 patients with ONJ, 60% with minor invasive surgery or with local disinfectants and antibiotics, while the remaining 40% were treated radically with bone resection up to viable bone. Thirty-eight percent of the conservative group were classified as responsive compared with 86% responded to treatment in the radical group.^{7,21} Favia and colleagues also treated a 65-year-old female for ONJ 4 months after implant placement by en-block resection and no signs of recurrence were seen after a 20-month follow-up. Both conservative and aggressive methods have shown to be effective; however, more studies must be performed to determine the better methodology.¹⁰ In our study, all patients were surgically treated under general principles and successfully treated. During sequestrectomy procedure, oval-shaped carbide bur was used to grind the necrotic bone and infected jawbone. Complete resection should be preformed until fresh blood is coming from bone marrow. Using other instruments such as piezosurgery or ultrasonic devices takes more time and cannot resect the basal bone, so low-speed rotary instrument is the choice for sequestrectomy. In five patients (except No. 5), collagen and fibrin glue were used to cover the exposed bone. Because of the inflamed soft tissue overlying sequestrum, it is hard to get primary closure. Collagen and fibrin glue could act as scaffold during gingival healing.

One patient (No. 6) was recommended to extract her maxillary left canine at the time of her first surgery. She refused and the tooth was preserved. Six months later, her case progressed and the canine was extracted along with further resection of the osseous. It is advisable to eliminate all signs of disease during the first surgery to prevent further complications.

The time from implant surgery to jaw necrosis in the cases described in this paper was between 1 and 17 months. Five patients developed symptoms 1–4 months after surgery. It is recommended to place patients with a history of bisphosphonate use on a periodic follow-up schedule after implant surgery.

Bone exposure eventually results in necrosis and infection. It is better to do early surgical intervention to whom showed bone exposure after surgical dental procedure. The patient (No. 4) who underwent primary closure after bone exposure was successfully treated with advanced flap. However, the exposed bone needed to remove during implant uncovery surgery.

Despite the low risk of ONJ development after implant surgery in patients taking oral bisphosphonate, there are reports of ONJ in the maxilla and mandible after implant placement. Therefore, clinicians must be prudent to perform surgery in patients taking oral bisphosphonates. Informed consent and an explanation of the risk of osteonecrosis are mandatory prior to surgery. If a sign of infection is observed, early surgical intervention should be performed to prevent further extension of the lesion.

CONCLUSION

Although uncommon, osteonecrosis does occur with the use of oral bisphosphonate in patients who undergo dental implant surgery. Wide resection of necrotic bone, collagen graft, and primary closure are key factors for successful healing.

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