Clinical Report

The Use of a Piezoelectric Device for the Removal of a Sequestrum Involving the Inferior Alveolar Nerve in Patients with Medication-related Osteonecrosis of the Jaws: Evaluation of Clinical Outcomes with Comparison to a Conventional Device

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Abstract: The mandible is commonly disturbed by medication-related osteonecrosis of the jaws (MRONJ), and preservation of inferior alveolar nerve (IAN) function is critical after surgery. A piezoelectric device is an ultrasound instrument that can remove the bone without soft tissue damage. We evaluated the usefulness of the piezoelectric device for the removal of a sequestrum involving the IAN in MRONJ patients with comparison to a conventional device such as rotary burs. Piezoelectric device group (n=12) and conventional device group (n=8) were compared for age, sex, disease, medication, cause, stage, operation time, hospitalization, prognosis, and subjective neurological dysfunction of the mental region with a question. In the piezoelectric device group, the neurological function was also assessed objectively with neurosensory testing. Both groups were similar in age distributions and MRONJ stage. The piezoelectric device group tended to be associated with female patients with osteoporosis and those receiving oral bisphosphonates; however, no significant differences. A comparison of the clinical outcomes showed a tendency of the reduction in the operation time and hospitalization period in the piezoelectric device group; however, no significant difference. Almost good prognosis was obtained in both groups. Subjective neurosensory dysfunction of the mental region was observed in both groups at 1 week postoperation, but the incident rate was lower in the piezoelectric device group. At 8 weeks postoperation, no patients in the piezoelectric device group showed dysfunction while 2 patients in the conventional device group showed dysfunction. In the piezoelectric device group, objective neurosensory tests of the IAN showed 2 patients of dysfunction at 1 week postoperation, but improved within 4 weeks postoperation. Piezoelectric surgery safely removed the sequestrum adjacent to the IAN with good prognosis in MRONJ patients. Our results indicate that piezoelectric surgery may be helpful in shortening the operation and hospitalization time, and reducing the risk of nerve injury.

Key words: Mandible, Inferior alveolar nerve, Medication-related osteonecrosis of the jaws, Sequestrum, Piezoelectric surgery

Introduction

Osteonecrosis of the jaw (ONJ) is defined as exposed bone in the maxillofacial region that does not heal for 8 weeks in patients with no history of craniofacial radiation1-3). ONJ was first reported in patients receiving bisphosphonate (BP) therapy2, and a number of patients with BP-related ONJ (BRONJ) have been described. Furthermore, reports have shown that the administration of denosumab can also cause ONJ4). The American Association of Oral and Maxillofacial Surgeons (AAOMS) propounds that ONJ triggered by anti-resorptive medications (i.e., BPs and denosumab) and anti-angiogenic medications is defined as medication-related ONJ (MRONJ)5). Although the etiology of MRONJ is not fully understood, potential mechanisms affecting MRONJ include inhibition of osteoclastic bone resorption and remodeling, soft tissue toxicity, inhibition of angiogenesis, inflammation and infection, and immune dysfunction5).

Recent studies have indicated that surgical therapy is more effective than conservative therapy in MRONJ patients7-9). The mandible is more commonly disturbed by MRONJ than the maxilla7-9), and in cases of operation, preservation of inferior alveolar nerve (IAN) function is critical for maintaining quality of life10). Generally, the precise removal of bone in close vicinity to the IAN is difficult when using conventional instruments, such as rotary burs.

The piezoelectric device is an ultrasound instrument used to remove bone with microvibrations11-12). The benefit of this device is its ability to selectively cut only mineralized structures without damage to soft tissue11, 12). Microvibrations, of 60–210 μm at 25–29 kHz, are adapted to mineralized tissue while soft tissue remains uninjured under these conditions. This allows for easier intraoperative management and accurate bone cutting13). The device is easier to control in comparison to rotary...
burs or oscillating saws because there is no requirement for an additional force to oppose the rotation or oscillation of the device. In addition, ultrasonic vibrations breakdown the irrigation water into small particles that wash away from the field of operation, producing a bloodless area, thus allowing greater intraoperative visibility. The use of piezoelectric surgery in the field of oral and maxillofacial surgery has increased, and the usefulness in MRONJ surgery has also been reported. However, to the best of our knowledge, the use of a piezoelectric device in the mandibular sequestrectomy of MRONJ with evaluation of IAN function has not been reported. In this study, we evaluated the usefulness of the piezoelectric device for the removal of a sequestrum involving the IAN in patients with MRONJ, and examined the clinical outcomes and compared them against those associated with a conventional device. We also discuss the efficiency of piezoelectric surgery for mandibular sequestrectomy in MRONJ patients.

Materials and methods

Clinical data

We retrospectively investigated patients who underwent surgical treatment of MRONJ involving the IAN at the Department of Dentistry and Oral Surgery at the University of Fukui Hospital from October 2008 to September 2018. Sixty-six patients with MRONJ were identified, of which 42 patients had lesions only in the mandible. Of the 42 patients examined, 22 patients were excluded due to patients receiving conservative treatment only (10 patients), no involvement of the IAN during operation (8 patients), the presence of neurosensory dysfunction before surgery (2 patients), and radical surgery with mandibular segmental resection (2 patients).

Based on the device used for sequestrectomy, the 20 patients involved in this study were assigned to either the piezoelectric device (Piezosurgery®; Mectron Medical Technology, Carasco, Italy) group (n=12), or the conventional device group (n=8). The operation was completed via the intraoral approach under general anesthesia (18 patients) or local anesthesia (2 patients). The mucoperiosteal flap was reflected, and the granulation tissue and sequestrum were removed. If the lesion contained teeth, they were extracted. The bone in the disturbed area was removed using rotary burs until vital bleeding was confirmed at all margins. The sequestrum near the IAN was removed using the piezoelectric device or conventional device: rotary burs (Fig. 1). After the surgical areas were thoroughly irrigated with saline water, defects were closed with sutures in all cases. The operations were performed under the instructions of an oral surgery specialist. Antibiotics were administered to all patients. In cases of neuropathy of the mental region after surgery, oral administration of vitamin B12 (mecobalamin 1,500 μg/day) was continued until symptoms improved. All patients received follow-up until total mucosal coverage of the wound was achieved.

Both groups were compared for characteristics such as age, sex, disease, MRONJ-related medication, cause, and stage. We also examined the cessation of medication, surgical time, duration of hospitalization, and prognosis. The prognosis was evaluated according to the following diagnostic criteria. Healed: complete mucosalization of the exposed bone was achieved, with pain relief; Improved: the patient was symptomatically better or moved to a lower stage; Stable: the disease had not progressed to a higher stage; Worse: the patient demonstrated progressive pain, infection, or persistent bone exposure, with advancement to a higher stage. The neurological dysfunction of the IAN was assessed subjectively with a question. In the piezoelectric device group, the neurological dysfunction of the IAN was also examined objectively with neurosensory testing using the Semmes-Weinstein test, two-point discrimination, the pinprick test, and thermal discrimination. In the Semmes-Weinstein test, a score greater than 2.83 represented neurosensory dysfunction. In the two-point discrimination assessment, a score greater than 15 mm or out of the preoperative range represented neurosensory dysfunction.

This study was approved by the Institutional Research Board of Ethical Committee of the University of Fukui, Faculty of Medical Sciences (No. 20180110).

Statistical analysis

Statistical analyses were performed using StatMate software (version 1.1, ATMS Co., Ltd., Tokyo, Japan; for Macintosh). The values are presented as the mean with standard deviation (SD). Differences between groups were evaluated with unpaired t tests. Correlations between categorical variables were assessed by Chi-square or Fisher’s exact test. The results were considered statistically significant at P < 0.05.

Results

Twenty patients (4 men and 16 women) were analyzed (Table 1). The youngest patient was 29 years old and the oldest was 91 years old. Five patients had oncologic disease and 15 patients had osteoporosis. Fourteen of the 15 patients with osteoporosis were women. All patients had been treated with anti-resorptive medications: 11 patients had received oral BPs, 4 patients had received intravenous BPs, 4 patients had received denosumab, and 1 patient had received both oral BP and denosumab. Seventeen patients displayed typical initiating causes of MRONJ, i.e., tooth extraction, periodontitis, and ill-fitting dentures. In all cases, MRONJ occurred in the mandible without neurosensory dysfunction of the mental region. Sixteen patients were diagnosed with MRONJ stage 2 and 4 patients were diagnosed with MRONJ stage 3. All patients received surgical therapy after an appropriate drug holiday of MRONJ-related medication.

Comparing patient characteristics and clinical outcomes (Table 2), there was no significant difference between groups in age or MRONJ stage. The piezoelectric device group tended to be associated with female patients with osteoporosis and those receiving oral bisphosphonates; however, there were no significant differences. Comparison of the clinical outcomes showed a tendency of reduced operation time and hospitalization period in the piezoelectric device group; however there were no significant difference. Almost good prognosis was obtained in

Figure 1. The tips of the devices used in this study. (A) Piezoelectric device. Upper: OP3, middle: OT7, lower: OT5. (B) Conventional device. Upper: cutting bur, lower: diamond bur.
Table 1. Characteristics of patients

| Case | Age | Sex | Disease | Medication | Cause | Site | *Neurosensory disturbance of mental region | **Stage |
|------|-----|-----|---------|------------|-------|------|------------------------------------------|---------|
| Piezoelectric device group | | | | | | | | |
| 1   | 78  | F   | Osteoporosis | Denosumab | Tooth extraction | Mandible | No | 2 |
| 2   | 76  | F   | Osteoporosis | Risedronate | Periodontitis | Mandible | No | 2 |
| 3   | 68  | M   | Osteoporosis | Minodronate | Unknown | Mandible | No | 2 |
| 4   | 81  | F   | Osteoporosis | Denosumab | Tooth extraction | Mandible | No | 2 |
| 5   | 58  | F   | Osteoporosis | Risedronate | Tooth extraction | Mandible | No | 2 |
| 6   | 85  | F   | Osteoporosis | Risedronate | Tooth extraction | Mandible | No | 2 |
| 7   | 29  | F   | Giant cell tumor | Zoledronate | Tooth extraction | Mandible | No | 3 |
| 8   | 91  | F   | Osteoporosis | Risedronate, Denosumab | Periodontitis | Mandible | No | 3 |
| 9   | 78  | F   | Osteoporosis | Denosumab | Tooth extraction | Mandible | No | 2 |
| 10  | 77  | F   | Osteoporosis | Minodronate | Tooth extraction | Mandible | No | 2 |
| 11  | 67  | F   | Osteoporosis | Minodronate | Tooth extraction | Mandible | No | 2 |
| 12  | 80  | F   | Osteoporosis | Ibandronate | Tooth extraction | Mandible | No | 2 |
| Conventional device group | | | | | | | | |
| 1   | 69  | F   | Osteoporosis | Risedronate | Ill-fitting denture | Mandible | No | 2 |
| 2   | 48  | F   | Breast cancer, bone metastasis | Zoledronate | Periodontitis | Mandible | No | 3 |
| 3   | 80  | F   | Osteoporosis | Risedronate | Periodontitis | Mandible | No | 2 |
| 4   | 81  | M   | Prostate cancer, bone metastasis | Zoledronate | Unknown | Mandible | No | 2 |
| 5   | 69  | M   | Prostate cancer, bone metastasis | Zoledronate | Tooth extraction | Mandible | No | 2 |
| 6   | 75  | F   | Osteoporosis | Ibandronate, Risedronate | Tooth extraction | Mandible | No | 2 |
| 7   | 86  | F   | Osteoporosis | Risedronate | Tooth extraction | Mandible | No | 2 |
| 8   | 77  | M   | Prostate cancer, bone metastasis | Denosumab | Unknown | Mandible | No | 3 |

*Subjective examination (preoperation).

**Classified according to the criteria described by Ruggiero et al. 1)

Figure 2. Clinical presentation (piezoelectric device group, case no. 10). (A) A panoramic radiograph showing radiolucency with diffuse irregularity in the left mandible (arrowheads). (B) A coronal CT image showing the formation of the bone sequestrum and bone destruction involving the left mandibular canal and close to the mental foramen (arrowhead: bone sequestrum, arrow: mental foramen). (C) A bone scintigraphy ($^{99m}$Tc) image showing increased uptake in the left mandible. (D) Intraoperative image showing removal of the sequestrum with the piezoelectric device near the IAN.
both groups after the operation. The neurological function of the IAN was assessed subjectively with a question. In both groups, neurosensory dysfunction of the mental region was observed at 1 week postoperation; however, the incident rate was lower in the piezoelectric device group. At 8 weeks, no patients in the piezoelectric device group showed dysfunction while 2 patients in the conventional device group showed dysfunction.

In the piezoelectric device group, neurological function of the IAN was examined subjectively as well as objectively with neurosensory testing (Table 3). Postoperative subjective symptoms of numbness or tingling in the mental region was observed in 4 patients; the dysfunction disappeared by 8 weeks postoperation. In the objective examination, 2 patients showed abnormal scores in the Semmes-Weinstein test, two-point discrimination, or thermal discrimination. Of these 2 patients, 1 patient improved after 2 weeks and another improved after 4 weeks postoperation, respectively.

Clinical presentation (piezoelectric device group, case No. 10)
A 77-year-old female was referred to our hospital in February 2018 because of an unhealed wound at the left mandible. She had undergone
tooth extraction of the left lower second premolar by a general dentist 1 month earlier. She did not drink alcohol and was a non-smoker. Her medical history showed diabetes and osteoporosis, and she had no history of radiation therapy for the head and neck area. She had been treated with minodronate since January 2009.

Physical examination revealed no swelling of the face and no paresthesia of the left mental region. An intraoral examination showed a deliscence of the gingival mucosa in the lower left premolar with a size of 5 mm. Redness and pus discharge were observed, and exposure of the underlying bone was confirmed by inserting a sound. A panoramic radiograph presented radiolucency with diffuse irregularity in the left mandible (Fig. 2A). A coronal computed tomography (CT) image (bone window setting) showed the formation of bone sequestrum and bone destruction involving the left mandibular canal and close to the mental foramen (Fig. 2B). A bone scintigraphy (99mTc) image showed increased uptake from the left mandible (Fig. 2C). The patient’s history and clinical and radiographic findings were consistent with MRONJ. After consultation with the orthopedic surgeon, the administration of minodronate was discontinued for 2 months. Over 8 weeks, the patient showed no change in the bone exposure. In May 2018, she underwent intravenous administration of antibiotics (ampicillin 2 g/day), starting 2 days before surgery. The mandibular sequestrectomy was performed through an intraoral approach under general anesthesia. After the buccal and lingual mucoperiosteal flaps were reflected, granulation tissue and sequestrum were removed with curettes. The cortical bone of alveolar process and mucoperiosteal flaps were reflected, granulation tissue and sequestrum were removed with curettes. The cortical bone of alveolar process and bone destruction involving the left mandibular canal and close to the mental foramen were removed using rotary burs until vital bleeding was encountered at all bone margins. Sequestrum near the IAN was removed using the piezoelectric device (Fig. 2D). After the surgical area was thoroughly irrigated with saline, the wound was completely closed with sutures.

The postoperative course was uneventful. The intravenous administration of antibiotics (ampicillin 2 g/day) was continued for 6 days. Thereafter, antibiotics (amoxicillin 750 mg/day) were administered orally for 3 weeks. A histological examination showed sequestrum, necrotic tissue, and granulation tissue and the final diagnosis of MRONJ was confirmed. The neurological dysfunction of the IAN was assessed both subjectively with a question and objectively with neurosensory testing. Subjectively, paresthesia of the mental region was observed 1 week postoperatively; however, considerable improvement was found 1 month postoperatively and the paresthesia disappeared 2 months postoperatively. In the objective examination, the Semmes-Weinstein test, two-point discrimination, the pinprick test and thermal discrimination showed normal function of the IAN, even 1 week postoperation. There was no evidence of complications 5 months postoperation.

**Discussion**

MRONJ is one of the most severe complications in patients with cancer or osteoporosis using anti-resorptive or antiangiogenic medications. In our study, there was a tendency for the development of MRONJ in the mandible of elderly patients. The anatomical differences between the mandible and the maxilla might affect the development of MRONJ. Another report showed that osteonecrosis occurs more often in the mandible than the maxilla at a ratio of 2:1, and is associated with a difference in the blood supplies between both jaws and the existence of a thick cortical bone and medullary cavity in the mandible. With regard to elderly patients, the number of patients with cancer and osteoporosis has increased with the ageing population, and a concomitant increase in MRONJ patients has occurred. In our study, dental extraction or inflammatory dental disease was an important cause of MRONJ, similar to previous reports.

The management of MRONJ is challenging for professionals. Although the treatment guideline supports conservative management of ONJ, conservative therapy may not always lead to complete resolution of lesions. MRONJ patients who do not respond to conservative therapy occasionally display severe conditions due to prolonged infection. A previous report showed that the success rate of conservative treatment ranges from less than 20% to above 50%, which is considerably lower than the therapy success rate of over 85% reported for surgical treatment, and the authors advocate for surgical interventions to be considered at all MRONJ stages. Another report demonstrated that patients who received surgical treatment for MRONJ were 28 times more likely to have a positive outcome than nonsurgical treatment. In our study, all patients obtained the almost good prognosis after the operation. The appropriate treatment plan should be decided in accordance with individual patients' conditions.
with the condition and situation of the patient.

Piezoelectric surgery is based on modulated ultrasonic vibration of a tip, and is characterized by three features: 1) precise cutting due to horizontal and vertical vibration of the tip; 2) selective cutting, since the vibration frequency cuts mineralized but not soft tissue; and 3) a relatively blood-free surgical field due to the air-water cavitation effect. Thus, piezoelectric surgery offers precise, safe, and clean cutting of bone structures while maintaining the integrity of adjacent soft tissue. In this study, the piezoelectric device group showed a tendency for a shorter operation time. Generally, the bone cutting ability of the piezoelectric device is inferior compared to a conventional rotary bur, so operation time is increased if every procedure is performed with this device. To avoid the time loss, we performed surgery with the piezoelectric device only near the IAN. In orthognathic surgery, piezoelectric osteotomy reduced surgical time because fewer maneuvers were required to protect the soft tissue and a cleaner surgical field with increased visibility was produced.

In this study, the piezoelectric device group also showed a shorter hospitalization period. A previous report showed that the piezoelectric device did not injure osteocytes during the harvesting of bone particles from an intra-oral site for autogeneous bone grafting. Microscopic examination of the collected bone particles revealed outgrowth and differentiation of osteoblasts, identified by histochemical staining of alkaline phosphatase activity and immunohistochemical staining for osteocalcin. The osteogenesis was consistently more active in bony samples from implant sites that had been prepared using the piezoelectric device compared to a conventional drill, and that there was an earlier increase in bone morphogenetic protein-4 (BMP-4) and transforming growth factor-β2 (TGF-β2) mRNA, and fewer pro-inflammatory cytokines of tumor necrosis factor-α (TNF-α) mRNA in the bone around the implants. Thus, piezoelectric surgery is more effective in bone healing by stimulating bone remodeling and controlling inflammation. In summary, piezoelectric surgery does not damage soft tissue and inhibit bone healing, and may promote a more comfortable postoperative healing process and shorter hospitalization.

Injury of the IAN causes skin numbness of the lower lip and chin, as well as devitalization of the teeth. Thus, maintaining IAN function is important for quality of life. In this study, the neurological dysfunction of the IAN was assessed subjectively with a question. In the examination of neurosensory function related to IAN lateralization in 87 patients, the mean duration of full recovery was 37 ± 15 days. We investigated the IAN at 1 and 8 weeks postoperation, and the piezoelectric device group showed earlier improvement. In an experimental report, the use of piezoelectric device for transposition of the IAN produced roughening of the epineurium with no affection on deeper structures and induced less damage than a conventional rotary bur. Another report also showed that exposure of the nerves to the piezoelectric device did not dissect the nerve but only induced some structural damage. Our results and these reports collectively suggest that the piezoelectric device is effective in surgery near the IAN.

In the piezoelectric device group, we also examined neurological conditions of the IAN with objective neurosensory testing. Fewer patients showed objective dysfunction than subjective symptoms. In addition, improvement of subjective symptoms of the mental paresthesias was observed immediately after improvement of objective examination. Previous reports showed that the level of subjective complaint was markedly higher when compared with the objectively-tested level of deficit, and higher detection of subjective symptoms of neurosensory disturbance than objective examination. These reports may explain our results in this study. In the piezoelectric device group, the observed neurological IAN injury was temporary. This result highlights the atraumatic effects of the piezoelectric device for the IAN, even in MRONJ patients. In this study, the number of cases was small, thus larger samples are needed to elucidate the efficacy of piezoelectric device.

In conclusion, to the best of our knowledge, this is the first study on the use of a piezoelectric device in mandibular sequestrectomy of MRONJ with evaluation of IAN function. Piezoelectric surgery was shown to safely remove the sequestrum adjacent to the IAN with good prognosis in MRONJ patients. Our results also indicated that the piezoelectric device may be helpful for shortening the operation and hospitalization time, and reducing the risk of nerve injury.

Conflict of Interest

The authors declare no conflict of interest.

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