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Original Research

Evaluation and comparison of CT values in bisphosphonate-related osteonecrosis of the jaw

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ABSTRACT

Objective: This purpose of this study was to investigate whether CT is useful for diagnosing BRONJ by comparing CT findings in BRONJ patients.
Methods: CT images of the mandible were obtained from a total of 14 patients with BRONJ, 14 patients treated with BPs and 14 control patients. In each patient, 15 transaxial CT images were selected and 30 configured regions of interest (ROI) were identified. We measured the CT values in the interdentium mandibular region between the bilateral second molars. On the axial CT images, CT measurements were obtained in the mesiodistal direction in order to assess the widest diameter of osteolysis/sequestrum.
Results: Regarding the total area, the CT values in the BRONJ group were higher than those observed in the bisphosphonate treatment group ($P = 0.011$), which were higher than those observed in the control group ($P = 0.014$). There were no significant differences between the sites with and without BRONJ development in the incisal areas ($P = 0.13$); however, there was a significant difference in the molar areas ($P = 0.001$).
Conclusions: Assessing the molar area is more useful than assessing the incisal area for evaluating BRONJ. Measuring of CT values may be useful for diagnosis and early detection of BRONJ.

1. Introduction

Bisphosphonates (BPs) constitute a group of pharmacological agents used as anti-osteoclastic, anti-resorptive drugs in patients with calcium metabolism disorders, such as osteoporosis, multiple myeloma, Paget's disease and hypercalcemia of malignancy [1]. Licata and Michaelson and Smith noted that the most important effect of these pharmacological agents is to promote the apoptosis of osteoclasts [2,3]. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) was first reported by Marx et al. [4], who suggested implying that the destruction of the vascular complexity of the jaw mediated by the use of BPs is responsible for necrosis and secondary infection of the bone matrix [4]. Since first described in 2003, several hundred cases of BRONJ have been published. The diagnostic criteria for BRONJ developed by the American Association of Oral and Maxillofacial Surgeons in 2007 include a history of BP use, the absence of radiotherapy to the head/neck and the presence of exposed bone in the maxilla or mandible persisting for more than 8 weeks [5,6].

Several studies have reported that this condition affects different tissue and cell types. For example, BPs inhibit osteogenic cells, osteoclasts and human fibroblasts [7,8]. Furthermore, BPs restrict vasculogenesis and angiogenesis via inhibition of the cell function of endothelial progenitor cells and mature endothelial cells and reduce the viability of oral keratinocytes, leading to impaired mucosal wound healing [9,10]. In addition, a reduction in extracellular matrix protein production has been described, and there is a standard position paper on this issue from the Japanese Society of Oral and Maxillofacial Surgeons [11]. Bone turnover is suppressed excessively by the administration of BP drugs. The accumulation of micro-fractures in the mandible and the suppression of angiogenesis induce necrosis and the apoptosis of bone cells. Although there are various theories regarding the mechanisms underlying this phenomenon, the exact etiopathology of BRONJ has not been investigated in detail.

☆ Asian AOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

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Current therapeutic strategies only aim to control the symptoms of BRONJ, and radical removal of necrotic bone is limited to severe cases [12,13]. Physicians often agonize over the diagnosis of BRONJ, and it is difficult to properly identify the region of BRONJ using imaging. Currently, effective cause therapy for BRONJ is not available, although several treatment modalities have been reported, including conservative medical management, various types of surgery, hyperbaric oxygen, ozone therapy and laser therapy.

The past literature has examined the pathology of BRONJ using CT imaging; however, the relationship between CT values and the diagnosis of BRONJ has not been assessed, and it is difficult to conduct an image evaluation using CT [14]. On the other hand, CT is capable of providing detailed information regarding morphological changes based on numerical values (expressed in Hounsfield units (HU)) of the linear attenuation coefficient of bone density in selected locations. CT values are also capable of describing bone density. We previously evaluated the degree of bone healing after intraoral vertical ramus osteotomy using CT values [15]. Our results showed that CT values are useful in evaluating morphology; therefore, we sought to examine the relationships between CT values and the pathogenesis of BRONJ.

Hamada et al. reported that the CT values should be measured to the mandible in BRONJ patients and found significant differences between the BRONJ group and the control group in terms of the cancellous bone CT values in their study [16]. However, the percentages of cancellous and cortical bone with respect to the bone width of the mandible differed between the incisal and molar areas. Indeed, bone lesions, such as those involving osteomyelitis, are more difficult to clinically assess in the incisal area than in the molar area. We therefore measured the CT values in patients with BRONJ and investigated the differences in CT values between the incisal and molar areas. We also investigated the CT values in the non-BRONJ patients receiving BP treatment. This purpose of this study was to investigate whether CT values are useful for diagnosing BRONJ by comparing CT values in these patients.

2. Methods

2.1. Subjects

This study was a nonrandomized, retrospective (historic) cohort study of patients. Therefore, the present study was granted exemption of institutional review board approval by our institution.

A total of 14 patients (2 males and 12 females) were diagnosed with BRONJ according to the diagnostic criteria of the American Association of Oral and Maxillofacial Surgeons (AAOMS) based on clinical and radiographic examinations conducted at Kobe University Hospital and Kakogawa East City Hospital in the department of oral and maxillofacial surgery between February 2006 and December 2013. BRONJ patients have exposed bone in the oral cavity despite receiving 8 weeks of adequate treatment, with no evidence of local metastasis and no prior history of radiotherapy to the affected region [5].

2.2. Methods

2.2.1. BRONJ diagnostic criteria

The definition of BRONJ was described according to the American Association of Oral and Maxillofacial Surgeons position paper [6]. BRONJ is diagnosed based on the following three characteristics: (1) current or previous treatment with a BP; (2) the presence of exposed bone in the maxillofacial region persisting for more than 8 weeks; (3) no history of radiation therapy to the jaw.

2.2.2. Patient characteristics

The subjects were selected from the patients who visited the Kobe University Hospital or Kakogawa East City Hospital Oral and Maxillofacial Surgery between February 2006 and March 2014, were diagnosed with BRONJ in the mandible and had undergone CT imaging. Simultaneously, the patients in the BP treatment group were those observed without lesions in the mandible and had undergone CT of the mandible for any reasons. The patients in the control group never received treatment with BP, had no systemic disease, and no lesions in the mandible. The BRONJ subjects included 14 patients (2 males and 12 females), among whom nine received oral BP therapy and five received BP injections. The period of administration of the BP drug was less than 3 years in seven patients and more than 3 years in seven patients. The patients' ages ranged from 54 to 81 years, with a mean age of 72.6 years. The BRONJ stage was Stage 1 in three patients, Stage 2 in seven patients and Stage 3 in four patients. The other treatment group included nine patients who received oral BPs and five patients who received BP injections (six males and eight females) with other diseases but without mandibular bone lesions. The period of administration of the BP drug was less than 3 years in 11 patients and more than 3 years in 3 patients. The patients' ages ranged from 46 to 91 years, with a mean age of 67.6 years. The control subjects included 14 patients who did not receive BP therapy (6 males and 8 females) and had no jaw bone lesions. The patients' ages ranged from 51 to 83 years, with a mean age of 70 years (Table 1).

2.2.3. Bisphosphonate treatment

The three types of bisphosphonates used in this study were alendronate, risedronate and zoledronate. At the onset of BRONJ, six patients were being treated with alendronate, three were receiving risedronate and five were receiving zoledronate for the treatment of osteoporosis or cancer. The median duration of bisphosphonate treatment was 31.4 months (range: 7–72 months). In the bisphosphonate treatment group consisting of patients without BRONJ non-onset, five patients were being treated with alendronate and four were receiving risedronate for the treatment of osteoporosis or cancer or as prophylactic therapy. The median duration of bisphosphonate treatment was 27.7 months (range: 10–75 months) until CT imaging.

2.2.4. Setting of CT

The CT examinations were performed at the time of diagnosis using the Aquilion64® system (Toshiba Medical Systems, Tokyo, Japan) at the Wakaba Imaging Support Center or Kobe University Hospital or Kakogawa East City Hospital (tube current: 100 mA; scanning time: 3 s; slice thickness: 0.5 mm; slice width: 0.5 mm; field of view: 25 cm). The slice plane was parallel to the occlusal plane and the scanned area extended from the floor of the orbit to the inferior border of the mandible.

2.2.5. Method of measurement

The measurements were obtained with reference to the method of Hamada et al. [16]. In each case, we measured the CT values in the interdentium mandibular region between the bilateral second molars. The measurement points avoided the teeth. In edentulous areas, we measured the points that assumed the mandible (Fig. 1). The CT values were measured in the vertical tomographic plane to the dental arch on the axial CT. On the tomographic images, the top 1/3 and bottom 1/3 of the mandible cancellous bone between the lower edge and alveolar crest and the lower edge was measured as the CT value. The CT values reflected the range of each point in a square 2.0 mm × 2.0 mm in size, and the mean of the measurements was calculated. With respect to the measuring process, a site that did not include tissue other than bone was selected in order to minimize the presence of artifacts. The BRONJ sites were