Influence of Periodontal Infection upon the Stage of MRONJ

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- ABSTRACT –

Influence of Periodontal Infection upon the stage of MRONJ

Periodontal diseases and dental diseases are proved as a significant role for Medication related osteonecrosis of the jaw(MRONJ) from many studies. But there has been no study of whether periodontal disease affects not only the onset of MRONJ but also the progression of MRONJ. Thus, The aim of this study is to prove the influence of periodontal infection upon the stage of MRONJ. This study included 86 patients diagnosed with MRONJ, who visited the Department of Dentistry, Oral & Maxillofacial Surgery at Ajou University Hospital from August 2006 to September 2016. Each patient with MRONJ was staged according to the 2014 American Association of Oral and Maxillofacial Surgeons(AAOMS) MRONJ position paper. Each patient's alveolar bone height was measured by panoramic radiography using Bjorn and Holmberg's method. There was a significant difference in the alveolar bone height between the MRONJ groups with and without MRONJ infection as seen by the independent t-test ($p = 0.004 < 0.05$). From this study, Periodontal infection can affect both the risk for developing MRONJ and also the MRONJ stage.

Key words : Bisphosphonate-Associated Osteonecrosis of the Jaw, Periodontal disease

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Ⅰ. INTRODUCTION

Bisphosphonates (BPs) are medications that inhibit osteoclasts and are used to treat bone cancers and osteoporosis. Although BPs improve bone mineral density and reduce the risk of fracture, some patients develop medication-related osteonecrosis of the jaw (MRONJ). Intravenous BPs are antiresorptive medication used to manage cancer-related conditions, including hypercalcemia of malignancy, skeletal-related events associated with bone metastases in the context of solid tumors such as breast, prostate, and lung cancers, and for management of lytic lesions in the setting of multiple myeloma. Although the potential for BPs to improve cancer-specific survival remains controversial, these medications have had a significant positive effect on the quality of life for patients with advanced cancer involving the skeleton. Intravenous BPs and oral BPs are approved for treatment of osteoporosis and osteopenia. But BPs can cause critical osteonecrosis of the jaw. It was first described from Marx in 2003.(Marx, 2003) In the 2014 American Association of Oral and Maxillofacial Surgeons (AAOMS) MRONJ Position Paper, MRONJ is defined as necrotic bone changes and delayed healing conditions in the mandible or maxilla that persists for more than 8 weeks in the context of current or previous treatment with an antiresorptive or antiangiogenic agent. MRONJ affects the patient's quality of life, producing significant morbidity. (Ruggiero et al., 2014) Signals and symptoms for MRONJ are pain, dental mobility, swelling in oral mucosa, soreness, and bone exposure.(Rasmusson and Abtahi, 2014) More recently, the Receptor activator of nuclear factor kappa-B ligand inhibitor is an antiresorptive agent denosumab, a new therapeutic agent for osteoporosis and bone metastasis, can also cause Osteonecrosis of the jaw(ONJ). (Japanese Allied Committee on Osteonecrosis of the et al., 2017)

BPs and other antiresorptive drugs, including denosumab, inhibit osteoclast differentiation and function and increase apoptosis, all leading to decreased bone resorption and remodeling. Osteoclast differentiation and function play a vital role in bone healing and remodeling in all skeletal sites, but ONJ occurs only primarily within the alveolar bone of the maxilla and mandible. An increased remodeling rate in the jaws may explain the differential predisposition to ONJ to occur in the jaws compared with other bones in the axial or appendicular skeleton. Long term studies in a large animal model have shown decreased intracortical bone turnover with dynamic histomorphometry. The central role of bone remodeling inhibition has been further corroborated by a similar incidence of ONJ observed with other antiresorptive medication including denosumab. Preliminary evidence has shown improved extraction socket healing in animals receiving systemic zoledronic acid(ZA) when treated with parathyroid hormone. This may be due to its positive effect on osteoclasts to increase bone remodeling. Systemic and local oral risk factors have been implicated in ONJ pathogenesis, in which several human studies have implicated dental disease or bacterial infection. Although tooth extraction was performed in most initial reported cases of ONJ, these teeth commonly had existing periodontal or periapical disease. From these clinical studies, several animal models have been developed to show that inflammation or bacterial infection and systemic antiresorptive drugs are sufficient to induce ONJ. Inflammation or infection has long been considered an important component of ONJ. Previous studies identified bacteria, especialy *Actinomyces* species, in biopsied specimens of necrotic bone removed from patients with ONJ. The presence of bacteria has prompted studies to evaluate the possibility of a complex biofilm on exposed bone. These studies have identified bacteria in combination with fungi and viruses, which may require more sophisticated therapies to

combat the multi-organism ONJ-associated biofilm.

Cases of MRONJ have been reported worldwide, including South Korea.(Hong et al., 2010) Well known MRONJ risk factors include steroid use, comorbid conditions, tobacco use, and periodontal disease. Several previous studies have shown a significant association between treatment with BPs and the incidence of MRONJ and alveolar bone loss. In presence of periodontal infection, oral bacteria gain access to the bone and can easily colonize the extraction socket. Thumbigere-Math et al. revealed that patients with MRONJ had more teeth with clinical attachment loss and more missing teeth compared with controls. (Thumbigere-Math et al., 2014) As a result of these researches, indicate that periodontal infection could be a possible risk factor in the development of MRONJ. Periodontal infection is a multimicrobacterial chronic infection, and the periodontal microbacteria are deverse and always dominated by anaerobic and facultative species as opportunistic pathogens. Furthermore, MRONJ is also known to occur more frequently in patients with gingival diseases and dental or gingival abscesses.(Kim et al., 2015)

However, there has been no study of whether periodontal disease affects not only the onset of MRONJ but also the progression of MRONJ. Thus, the aim of this study is to prove the influence of periodontal infection upon the stage of MRONJ.

Ⅱ. PATIENTS AND METHODS

A. Patients

This study included 86 patients diagnosed with MRONJ, who visited the Department of Dentistry, Oral & Maxillofacial Surgery at Ajou University Hospital from August 2006 to September 2016. Clinical and radiographic data were examined. Edentulous patients were excluded(1patient). Of the 86 participants, 11 were male and 75 were female, and they ranged in age from 42 to 90 years old (average 73.8). Patients were diagnosed with MRONJ using the criteria set forth in the 2014 AAOMS position paper [Table 1].

Table 1. Patient characteristics

	Number of Patients	Age (mean)
Stage 0	10	72.4
Stage 1	20	74.3
Stage 2	47	73.9
Stage 3	9	73.7

MRONJ stage distribution of Patients.

MRONJ stage 0 was defined by non-specific clinical findings and radiographic changes with no clinical evidence of bone necrosis. MRONJ stage 1 was defined by exposed and necrotic bone or a fistula that probes to bone in patients who are asymptomatic and have no evidence of infection. MRONJ stage 2 was defined by necrotic bone associated with infection, as evidenced by pain and erythema in the region of the exposed bone, with or without purulent

drainage. MRONJ stage 3 was defined by exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone resulting in a pathologic fracture, extra-oral fistula, oral antra/oral nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor (Ruggiero et al., 2014).

B. Method

a. Periodontal evaluation – Alveolar bone height

Each patient's alveolar bone height was measured by panoramic radiography using Bjorn and Holmberg's method, which expresses alveolar bone height as a percentage of the root length[Fig.1.]. Depicts the points and distances recorded from the panoramic radiographs. Point A was the root apex, which is defined as the apex of the palatal root for maxillary molars. Point A was positioned on two-rooted mandibular molars by bisecting the line connecting the apices of the mesial and distal roots (A1-A2). Points B and C represented the bone levels on the mesial and distal surfaces of each tooth, respectively. If a vertical osseous defect was evident radiographically, the bone level was defined as the most apical point of the defect. Tooth length was determined as follows: the midpoint of line BC was termed point D. Point E was defined as the point at which the line AD intersected the tracing of the occlusal or incisal edge. Tooth length was defined as the distance from point A to E. The mesial bone height was defined as the ratio AB/AE. The distal bone height was defined as AC/AE (Michalowicz et al., 1991). A full mouth bone score was obtained from each radiograph by averaging the mesial and distal proportional bone heights from all measurable teeth. Another periodontal indicator measured in this study was the residual tooth rate, which

was defined as the ratio of 28 over the total number of remaining teeth.

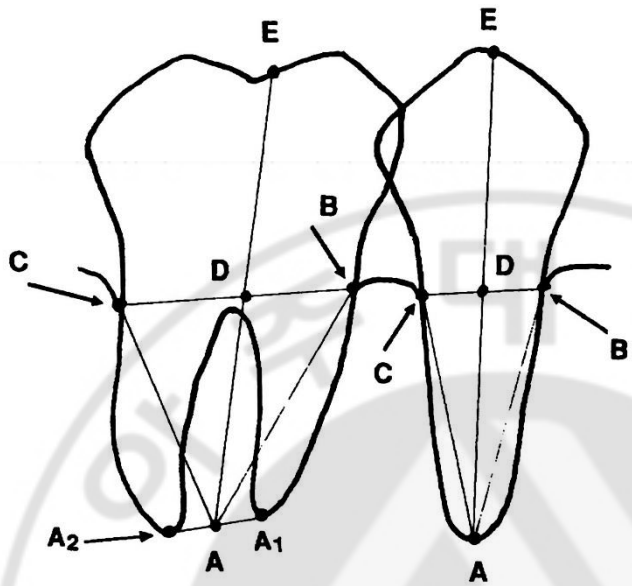

Fig.1. Method for measuring alveolar bone height.

Point A is the apex of tooth. Points B and C are alveolar bone levels. Point D is the midpoint of line BC. Point E is defined as the point at which the line AD intersects the tracing of the occlusal or incisal edge. The alveolar bone height is defined as the AD/AE ratio.

b. Statistical analysis

The SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The Kruskal-Wallis test and independent t-test were used for analyzing associations between alveolar bone height, residual tooth rate, and MRONJ stage. The significance level was defined by $p < 0.05$.

Ⅲ. RESULTS

Data were grouped according to MRONJ stages (1, 2, 3, and 4) and examined by the Kruskal-Wallis test. The alveolar bone height was significantly associated with the MRONJ stage (p = 0.009) [Fig.2.].

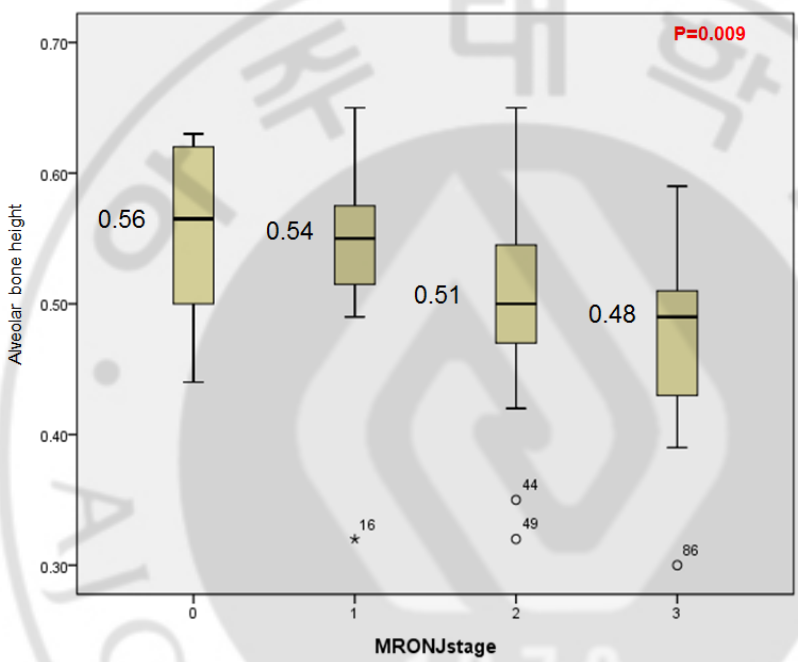

Fig.2. Statistical results of alveolar bone score and MRONJ stage.

Alveolar bone height is significantly associated with MRONJ staging by the Kruskal-Wallis test (p = 0.009)

To determine which groups were different, a Bonferroni post hoc analysis revealed a difference in alveolar bone height between patients with different stages of MRONJ. There was a significant difference in the alveolar bone height in patients with MRONJ stages 1 and 2 (p = 0.008). We then grouped the stages according to the presence or absence of infection: MRONJ stages 0 and 1 (without infection) were grouped together and MRONJ stages 2 and

3 (with infection) were grouped together. There was a significant difference in the alveolar height between the MRONJ groups with and without infection as seen by the independent t-test ($p = 0.004 < 0.05$) [Fig. 3.]. There was no significant difference in the residual tooth rate among MORNJ stages 0, 1, 2, and 3 [Fig. 4.].

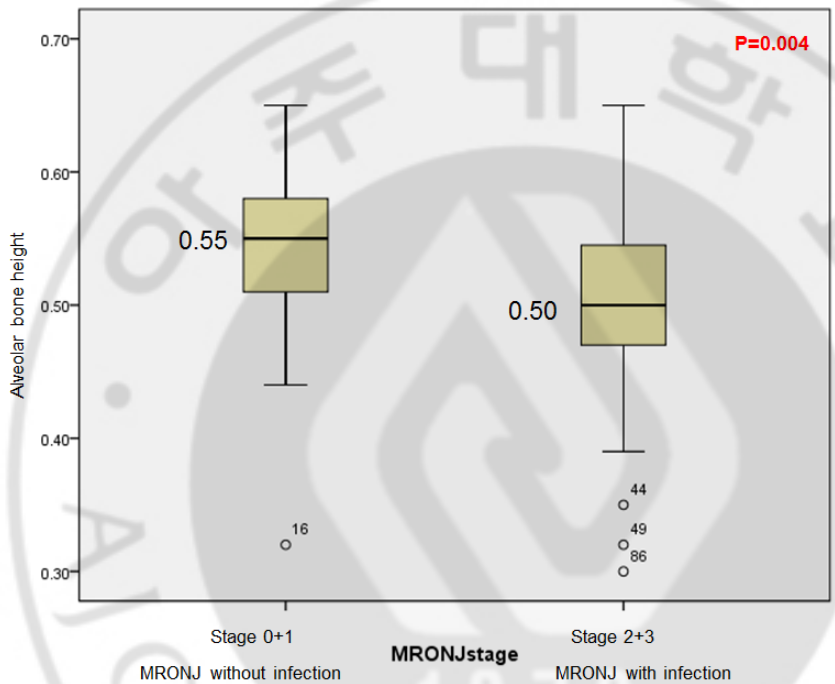

Fig.3. Statistical results of alveolar bone score and MRONJ stage 0,1 & 2,3 group.

Alveolar bone height is significantly associated with the presence or absence of infection in MRONJ by the independent t-test ($p = 0.004$).

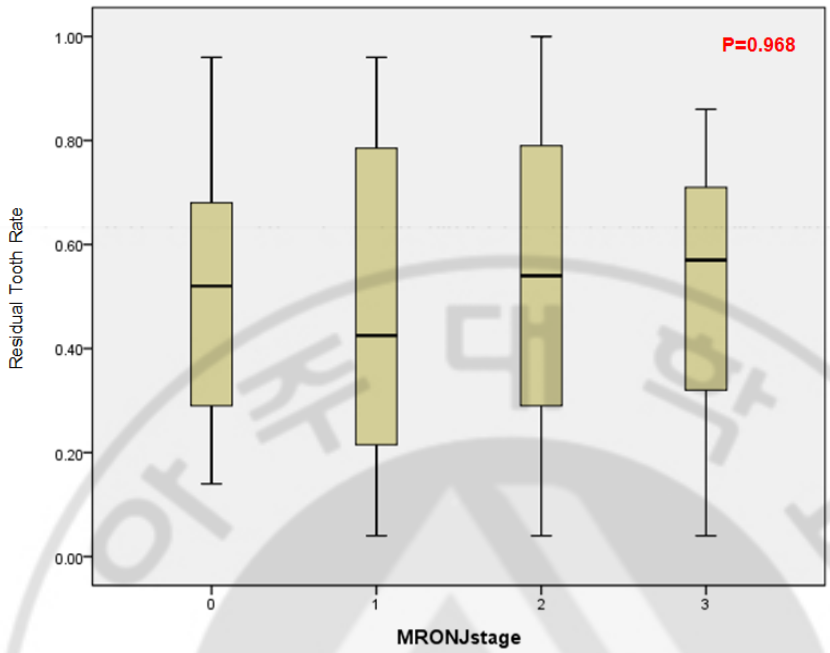

Fig.4. Statistical result of residual tooth rate and MRONJ stage.

Residual tooth rate was not significantly associated with the MRONJ stage by the Kruskal-Wallis test (p = 0.968)

Ⅳ. DISCUSSION

There are several well-known risk factors for developing MRONJ, including steroid use, comorbid conditions, tobacco use, and periodontal disease. Several previous studies have reported a significant association between BP therapy and the incidence of MRONJ and alveolar bone loss. (King and Umland, 2008) Yamazaki et al. noted a significant association between the incidence of BRONJ and alveolar bone loss in patients receiving intravenous BP therapy. (Yamazaki et al., 2012) Vivek et al. found that BRONJ patients had more missing teeth and less alveolar bone support compared to the non-BRONJ groups, suggesting that oral infections increase the risk for developing BRONJ. (Thumbigere-Math et al., 2014) Van Poznak et al. estimated that the risk of developing BRONJ is about 7 times higher in patients with a history of periodontal infection and dental abscesses. (Van Poznak and Estilo, 2006) In rat model of MRONJ, osteocyte necrosis precedes clinical bone exposure and osteonecrosis presented around teeth with severe periodontal disease. (Aghaloo et al., 2011) Patients with progressive periodontal disease increase the risk of developing MRONJ, and might benefit the management of periodontitis. (Li et al., 2016) The 2014 AAMOS MRONJ position paper listed pre-existing inflammatory dental diseases, such as periodontal disease or periapical pathology, as well-recognized risk factors for the development of MRONJ.

Based on the results of our study, periodontal infection may affect the stage of MRONJ. The alveolar bone score, reflecting the degree of periodontal disease, showed a significant association with the stage of MRONJ. Specifically, there was a significant difference in the alveolar bone height between patients with MRONJ stage 1 and stage 2. Using the independent t-test to compare the group including stages 0 and 1 and the group including stages 2 and 3, the alveolar bone height was significantly different. Therefore periodontal

infection may contribute to progressing from MRONJ stage 1 to stage 2. The crucial difference between MRONJ stages 0, 1 and stages 2, 3 is the absence or presence of infection. In the 2014 AAOMS MRONJ position paper, the signs of infection are not seen in stages 0 or 1, but the phrase 'with infection' specifically refers to stages 2 and 3. Alveolar bone height can be used as an indicator of the history of periodontitis, although a slight difference based on race and sex can have difference the measurement and affect MRONJ staging. The residual tooth rate did not show any association with the MRONJ stage. Factors influencing the residual tooth rate include congenitally missing teeth and extractions due to trauma or decay. Residual tooth rate is not related with the stage of MRONJ .

In this study, we found that periodontal infection can affect both the risk for developing MRONJ and also the MRONJ stage. This result is probably due to bacteria associated with periodontal diseases. In the patients with MRONJ state 2 and 3, there is an infection at the MRONJ site. The origin of this infection is still unclear. Multiple bacteria were found in cases of MRONJ, including *Fusobacterium nucleatum and Actinomyces*. (Mawardi et al., 2011) These bacteria are also associated with periodontal infections. Especiallly, *Actinomyces* were almost exclusively found attached to the necrotic bone**.** Once *Actinomyces spp.* invade tissues, they develop a chronic granulomatous infection characterized by the formation of tiny yellow clumps called sulfur granules. (Valour et al., 2014) These so-called sulfur granules were also found in the MRONJ with infections. Actinomyces was suggested an important role in the development of in the development of MRONJ and specific antibiotic treatment improves the prognosis of this process.(Arranz Caso et al., 2012) *Actinomyces naeslundii* is a member of commensal oral microbiota and dental plaque biofilm which may have some association with dental caries and periodontal diseases and

play an important role in the progression of periodontal diseases in severeal animal model. It has been commonly found in the lesions in patients with MRONJ.(Li et al., 2015) Tsurushima et al. investigated the involvement of Actinomyces specie in the development of MRONJ. They injected freeze-dried *Actinomyces actinomycetemcomitans* into the mandible marrow of Wistar rats pretreated with ZA. Histological osteonecrosis was extensively found in the mandibles of rats with *Actinomyces actinomycetemcomitans* inoculation and/or ZA treatment. In addition, the osteonecrosis area was much wider in rats treated with ZA and *Actinomyces actinomycetemcomitans* than that with ZA only.(Tsurushima et al., 2013)

In other researches, Sedghizadesh et al. observed *Fusobacterium* and *Treponema* by using electron microscopy.(Sedghizadeh et al., 2009) Finding bacteria associated with periodontal infection, such as *Fusobacterium nucleatum and Actinomyces*, suggests that these pathogens also affect MRONJ, however, this needs to be confirmed by further study. (Russmueller et al., 2016)

As we can see from the previous researches, There is a lot in common between bacteria with MRONJ infection and periodontal disease. Furthermore, this study reveals that there is significant association with alveolar bone height and the stage of MRONJ. It is not clear in which sequence and which bacteria influence the stage of MRONJ. Further research is also needed to determine whether bacteria present in periodontal infections affect both the induction and the progression of MRONJ to higher stages.

Ⅴ. CONCLUSION

BPs are widely used in clinics to treat metastatic cancer and osteoporosis. But this drug can occur Osteonecrosis of the jaw and it is a main adverse effect related to BPs. Once MRONJ appear in patient, they have severe inconveniences. It some patients, the irreversible degeneration of facial bone result in avascular osteonecrosis and need surgery.

In previous studies, periodontal diseases is an risk factor of MRONJ. but there has been no study of whether periodontal disease affects the progression of MRONJ. The result of this study suggest that periodontal infection influences both the risk of developing MRONJ and the progression of MRONJ to higher stages. Patients with MRONJ stage 2,3 have lower alveolar bone height compared with MRONJ stage 0,1. Surgeons should be aware the patients with periodontal disease can occur MRONJ and can get more worse the stage of MRONJ.

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– 국문요약 –

치주감염이 MRONJ 의 진행에 미치는 영향

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홍 윤 표

(지도교수: 이 정 근)

치주감염과 MRONJ 의 발병의 연관관계를 연구한 연구들에서 치주질환의 존재가 MRONJ 의 발병률을 높이는 것으로 보고되었다. 하지만 아직까지 치주질환이 MRONJ 의 진행에도 영향을 미치는지에 대한 연구는 없었다. 따라서 본 연구의 목적은 치주감염과 MRONJ 의 stage 의 상관관계를 분석하는 것이다. 본 연구는 2006 년 8 월부터 2016 년 9 월 사이에 아주대학교 치과병원 구강악안면외과에서 MRONJ 로 진단받은 86 명의 환자를 대상으로 하였다. 각각의 환자들은 2014 AAOMS 의 MRONJ position paper 의 기준에 따라 MRONJ 로 진단하였다. 환자들의 치주질환 정도는 방사선 사진에서 잔존치조골 높이를 Bjom 과 Holmberg 의 방법에 따라 측정하였다. 독립 t 검정 결과 치조골높이와 MRONJ 의 stage 관에 관계가 있는 것으로 분석되었다. 본 연구의 결과 치주감염은 MRONJ 의 발병 뿐 아니라 진행 정도에도 영향을 미치는 것으로 보인다.

핵심어 : 비스포스포네이트 턱뼈골괴사, 치주질환