

ORIGINAL**Relationship between oral condition and risk factors for jaw osteonecrosis in patients with hip fractures**

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Abstract : Purpose : Antiresorptive agents, such as bisphosphonates, are useful for the prevention of the recurrence of hip fractures. However, their administration has a risk of antiresorptive agent-related osteonecrosis of the jaw (ARONJ), and risk factors include poor oral hygiene. It is difficult for an orthopedic surgeon to examine a patient's oral condition thoroughly. This study evaluated the relationship between risk factors for ARONJ and intraoral findings in hip fracture patients. **Materials and Methods :** We evaluated 79 patients (average age of 82.2 years) with hip fracture surgery who underwent an oral assessment by dentists. The risk assessments of the intraoral findings were classified into four levels (levels 0-3), with levels 2 and 3 requiring dental treatment intervention. Data that could be extracted as risk factors of ARONJ were also examined. **Results :** Level 1 was found most frequently (54.4%), followed by level 0 (35.4%), level 2 (8.9%), level 3 (1.3%). The area under the receiver operating characteristic curve for the number of risk factors for the two groups (dental treatment intervention required and unnecessary) and oral findings were 0.732. When the cut-off value was set to two risk factors, the specificity and sensitivity was 53.5% and 87.5%. **Conclusions :** For hip fracture patients with a more than 2 risk factors, dental visits are recommended to prevent ARONJ. This is a useful evaluation method that can be used to screen for ONJ from data obtained from other risk factors, even if it is difficult to evaluate the oral condition in hospitals where dentists are absent. *J. Med. Invest.* 67: 328-331, August, 2020

Keywords : hip fracture, oral condition, osteonecrosis of the jaw, risk factor, dentist

INTRODUCTION

Globally, the aging population has been increasing, and in Japan, the aging rate is particularly rapid. In the future, people will live even longer, and it is estimated that 1/3 people in Japan will be over > 65 years old (1). Osteoporosis is one of the major disorders at risk of fractures and progresses with age. Hip fractures are a type of osteoporotic fracture and are frequently caused by low-energy trauma in osteoporotic patients (2). In addition to surgical treatment, it is crucial to administer antiresorptive agents, such as bisphosphonates, in the treatment of osteoporotic hip fractures (3). This drug therapy is useful for preventing osteoporosis relapse and improving life prognosis during the perioperative period (3, 4).

However, anti-receptor activator of nuclear factor κB ligand (RANKL) antibody preparations, which are classified as bone resorption inhibitors, and bisphosphonates have been shown to cause osteonecrosis of the jaw (ONJ) (5-7). Thus, the term antiresorptive agent-related ONJ (ARONJ) was adopted (8). Poor oral hygiene has been proposed by a position paper as a risk factor for ONJ (9). However, it is difficult for an orthopedic surgeon to determine the oral findings when initiating antiresorptive agent administration, and the oral findings require a dentist's examination. Therefore, if the risk factors of ARONJ can be

extracted from data other than a patient's oral hygiene status, it is considered that proactively recommending dental visits after orthopedic surgery to patients with several risk factors, even in hospitals where dentists are absent, could be implemented.

Therefore, the purpose of the present study was to evaluate the intraoral findings in the perioperative period of hip fractures and extract the risk factors for ARONJ.

MATERIALS AND METHODS*Patients*

This retrospective study was performed at the Department of Orthopedic Surgery and Oral and Maxillofacial Surgery, Kagawa Prefectural Central Hospital, Kagawa, Japan, and was approved by the ethics committee of Kagawa Prefectural Central Hospital (Approval No. 863). The registries of patients between 2018 and 2019 with hip fractures receiving surgical treatment, such as an open reduction and internal fixation or bipolar hemiarthroplasty (BHA), and whose oral status was evaluated during the perioperative period by a dentist at our hospital were retrospectively reviewed for possible inclusion in our study. All patients provided preoperative informed consent for undergoing surgical treatment of a hip fracture and for evaluating their oral condition during the perioperative period in the department of oral and maxillofacial surgery. All patients gave written consent to the inclusion of material pertaining to themselves and acknowledged that they could not be identified via this paper. We ensured that they were all fully anonymized. The inclusion criteria were a hip fracture treated with surgery and sufficient medical records available for review indicating an adequate

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medical condition and oral status. The exclusion criteria were a pathological hip fracture, patients who refused oral evaluation, and patients with insufficient medical information. The final study cohort consisted of 79 patients.

Risk factors for ONJ

The risk factors for ONJ were classified as patient (obesity, smoking, the presence of malignant tumor, hemodialysis, anemia, and diabetes), dental (a history of dental surgery), or drug (steroids, the administration methods of bisphosphonate [injection or internal use], human anti-RANKL monoclonal antibody, and chemotherapy for cancer) factors. Obesity was defined as a body mass index ≥ 30 kg/m², and anemia was defined as hemoglobin levels < 12 g/dL for women and < 13 g/dL for men, according to the World Health Organization guidelines (10). Diabetes was defined as $\geq 6.5\%$ HbA1c, according to the National Glycohemoglobin Standardization Program (11).

Outcome variables

The risk assessment results obtained from the oral findings were divided into two groups, which were clinically different in risk : level 0 and 1 (dental treatment unnecessary group) and level 2 and 3 (dental treatment necessary group). We analyzed the need for dentist intervention based on the number of risk factors and oral findings (Table 1).

Table 1. Risk classification based on intraoral findings for osteonecrosis of the jaw.

Level	Risk factors for osteonecrosis of the jaw considered from intraoral findings
0	Safe oral administration group, such as antiresorptive agents, with good oral hygiene and no oral lesions
1	Administrable group presenting local risk factors due to mild oral hygiene or non-infectious oral lesions, such as and mandibular protuberance
2	Careful administration group with local risk factors due to mild or poor oral hygiene and infectious lesions, such as mild periodontitis
3	Dosing avoidance group presenting risk factors due to poor oral hygiene and active infectious lesions due to pus

Data sampling

All data from the previous clinical records were examined with respect to the necessity of dentist intervention as an outcome variable and patient, dental, and drug factors as risk factors.

Statistical analysis

Data were recorded and entered using Microsoft Excel (Microsoft, Redmond, WA, USA) into an electronic database over the course of the study. The means and standard deviations were used when distribution was compatible with normality. Fisher's exact method and Pearson's chi-square test were used to analyze each group. An analysis of variance was conducted to compare the three groups. The database was transferred to JMP 11.2 software for Macintosh computers (SAS Institute, Cary, NC, USA) for statistical analysis. A P-value of < 0.05 was considered statistically significant.

RESULTS

The average age of the 79 patients in the study cohort was 82.2 years (range, 51-100 years), and included 61 women (77.2%) and 18 men (22.8%). The risk assessment for ONJ identified 28 patients (35.4%) as level 0, 43 (54.4%) as level 1, 7 (8.9%) as level 2, and 1 (1.3%) as level 3. Most patients were level 1, and 10.2% of the patients required dental intervention. Two patients among the level 2 patients were prescribed bisphosphonates without dental assessment before admission. One level 3 patient was newly administered bisphosphonate after admission before dental assessment. The risk factors included 60 patients with anemia (75.9%), 29 with malignant tumors (36.7%), and 11 with diabetes (13.9%). None of the patients were receiving intravenous infusions of zoledronic acid.

There were 13 patients who had been treated for osteoporosis prior to hospitalization, of which four were using bisphosphonates. None of the patients were using RANKL inhibitors. There was no significant difference between the predictive factors of the dental treatment necessary group and the unnecessary group (Table 2).

The number of risk factors averaged 1.8 per patient, with an

Table 2. Baseline characteristics of the study cohort.

Risk factor	Dental treatment unnecessary group (n = 71)	Dental treatment required group (n= 8)	P-value
Age (years)	82.4	81.5	0.78
Sex (male/female)	16/55	2/6	0.87
Smoking (%)	15.4	12.5	0.82
Malignant tumor (%)	33.8	62.5	0.11
Hemodialysis (%)	4.2	25	0.22
Anemia (%)	73.2	100	0.09
Diabetes (%)	11.3	25	0.12
Obesity (%)	1.4	0	0.73
History of dental surgery (%)	1.4	12.5	0.19
Chemotherapy (%)	1.4	0	0.89
Taking steroids (%)	2.8	12.5	0.17
RANKL inhibitors (%)	5.6	0	0.64
Oral bisphosphonate (%)	26.8	12.5	0.34
Intravenous bisphosphonate (%)	8.5	37.5	0.14

average of 2.5 for the dental intervention required group and 1.6 for the unnecessary group. There were 10, 29, 21, 11, 5, 2, and 1 patients with 0, 1, 2, 3, 4, 5, and 6 risk factors, respectively. The area under the receiver operating characteristic curve for the number of risk factors was 0.732 for the two groups (dental care intervention required and unnecessary) based on the oral risk assessment. When the cut-off value was set to two risk factors, the specificity was 53.5%, and the sensitivity was 87.5%, which was relatively high for screening (Table 3).

Table 3. Number of risk factors for osteonecrosis of the jaw and sensitivity specificity.

Sensitivity and specificity between the number of risk factors for osteonecrosis of the jaw and oral condition requiring dental intervention

Number of risk factor	Sensitivity (%)	Specificity (%)
1 or more	100	14.1
2 or more	87.5	53.5
3 or more	50.0	78.9
4 or more	25.0	90.1

DISCUSSION

In this retrospective study, we observed that 10.2% of the patients with hip fracture required dental intervention for the risk assessment of ARONJ. Moreover, for patients with more than 2 risk factors, dental visits are recommended to prevent ARONJ. In a clinical setting where hip fracture was treated, this is a useful and feasible evaluation method to screen for ARONJ with data obtained from the other risk factors except oral assessment.

Ideally, osteoporosis should be prevented before hip fractures occur, according to the International Society for Clinical Densitometry (12). However, osteoporosis is typically asymptomatic until a fracture occurs and is considered an age-related chronic disease characterized by a loss of bone mass and quality. Therefore, it is important to provide treatment for hip fracture patients to prevent subsequent fractures with increasing age. It is well known that the risk of subsequent hip fractures can be reduced by the initiation of osteoporosis treatment. It was reported that zoledronic acid significantly increased bone mineral density at the total hip by 5.5% (13). Furthermore, it significantly lowered the incidence of subsequent fractures at the hip by 33.8% (14). The use of antiresorptive agents for elderly hip fracture patients is highly beneficial. The patients with hip fractures in our study were elderly, with an average age of 82.2 years, and osteoporosis was diagnosed according to the Japanese Guidelines for Prevention and Treatment of Osteoporosis (15). Therefore, our study cohort comprised patients who required drug treatment for osteoporosis.

ONJ is a complication that should be considered when administering antiresorptive agents. In 2003, Marx first reported a new clinical entity, ONJ, in oncology patients who had received high-dose intravenous bisphosphonates (15). ONJ was then described in patients with osteoporosis who were administered low-dose oral bisphosphonates (16). In addition to bisphosphonates, past reports have described that another type of antiresorptive medication, RANKL inhibitors, such as denosumab, might also be associated with an increased incidence of ONJ (17). Numerous investigators have reported ARONJ in both basic and clinical studies. Although the precise pathogenesis of ARONJ remains unelucidated, the presence of infectious oral lesions and poor oral condition have been reported as risk factors

for the onset of ONJ (9, 18). The elderly population are prone to periodontitis and tend to experience a greater inflammatory insult to the alveolar bone (19, 20). It is essential to be able to safely initiate osteoporosis drug treatment by evaluating oral screening results. However, the oral cavity is complicated and includes lesions from the apex as well as periodontitis, and it is difficult for all orthopedic surgeons to perform an appropriate intraoral assessment in the same manner. Ideally, a dentist should be added to the Fracture Liaison Services team to further manage patient risk and prevent refracture. In reality, there are often no dentistry services available, so this would be difficult to achieve in all facilities. From this point of view, our examination of the relationship between oral risk factors and patient, dental, and drug factors is extremely significant and will aid in safe treatment in a hospital without dentists.

In the present study, the dental intervention group was considered to show an ONJ risk for the administration of antiresorptive agents. In previous reports, anemia and diabetes were considered as risk factors for developing ONJ (18). However, patients with hip fractures may present with anemia due to bleeding, making it difficult to grasp as an inherent risk factor for ONJ. The presence of malignant tumors may exacerbate the oral environment (21). However, it is often associated with other general conditions of the patient. In this study, there was no significant difference in the necessity of dental intervention among malignant tumor patients with hip fractures, and it was not an inherent risk. Thus, because various factors are involved in the oral condition, our method of judging from the number of risk factors was considered to be exceedingly meaningful.

It is challenging to pay multiple visits to the dentist after undergoing an operation for a hip fracture. Thus, it may not be possible to encourage all patients to visit a dental office. For this reason, it may be useful to recommend a dental visit to a patient with a high-risk factor of ≥ 2 with the cooperation of a family member or to request a visiting dentist. This is an important factor for orthopedists and co-medical staff in managing patients following discharge. It has been reported that patients who receive regular oral maintenance by dentists and those who maintain their oral environment were at low risk of developing ONJ, even if the dose of antiresorptive agents was increased (18). The Cochrane Systematic Review reported that the risk ratio was 0.10 (95% confidence interval 0.02-0.39) for the occurrence of ONJ every three months for oral care compared with standard care (22). This is also important from a long-term patient management perspective.

There are several limitations to this research. Firstly, an evaluation of the oral cavity for all surgically treated patients with hip fractures is not performed. Although it is conducted by a system that asks for a dentist, all patients could not be evaluated because of timing difficulties and obtaining consent from the medical staff. Secondly, the number of risk factors was simply calculated without considering the weighting of the risk factors. If there were a larger number of cases, it would be possible to conduct a more accurate study by comprehensively analyzing with a predictive score that considered the weighting of risk factors. It is hoped that more cases will be accumulated and studied in the future.

CONCLUSION

For patients with hip fracture with more than 2 risk factors, dental visits are recommended to prevent ARONJ. This is a useful evaluation method that can be used to screen for ONJ from other risk factors, even if it is difficult to evaluate the oral condition in hospitals where dentists are absent.

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DISCLOSURE OF INTEREST

The authors report no conflict of interest.

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