Diseases having an influence on inhibition of angiogenesis as risk factors of osteonecrosis of the jaw

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Abstract (J Korean Assoc Oral Maxillofac Surg 2016;42:271-277)

Objectives: The objective of this study was to retrospectively investigate the association of diseases having an influence on inhibition of angiogenesis such as hypertension, diabetes mellitus type II, hypercholesterolemia, and rheumatoid arthritis (RA) with the development of osteonecrosis of the jaws.

Materials and Methods: The 135 patients were allocated into 4 groups of bisphosphonate-related osteonecrosis of the jaw (BRONJ) group (1A); non-BRONJ group (1B); osteonecrosis of the jaw (ONJ) group (2A); and control group (2B), according to histologic results and use of bisphosphonate. This retrospective study was conducted with patients who were treated in one institute from 2012 to 2013. Fisher’s exact test and logistic regression analysis were used to analyze the odds ratios of diseases having an influence on inhibition of angiogenesis for development of ONJ.

Results: The effects of diabetes and hypertension were not statistically significant on development of ONJ. When not considering bisphosphonate use, RA exhibited a high odds ratio of 2.32 (P=0.094), while hyperlipidemia showed an odds ratio of 2.10 (P=0.144) for development of ONJ. More than one disease that had an influence on inhibition of angiogenesis showed a statistically significant odds ratio of 2.54 (P=0.012) for development of ONJ.

Conclusion: Patients without diseases having an influence on inhibition of angiogenesis were at less risk for developing ONJ.

Key words: Bisphosphonate-associated osteonecrosis of the jaw, Angiogenesis inhibitors, Rheumatoid arthritis, Hypercholesterolemia

I. Introduction

The concept of bisphosphonate-related osteonecrosis of the jaw (BRONJ) has evolved recently into medication-related osteonecrosis of the jaw (MRONJ). A recent position paper introduced two modifications to the definition. More specifically, anti-angiogenic agents were added to the list of medications, and "bone that can be probed" was considered equivalent to exposed bone.

Although the first case of BRONJ was reported several decades ago, the pathophysiology of MRONJ is not fully understood. There is controversy about the potential mechanisms underlying BRONJ pathophysiology among clinicians and researchers. The most widely accepted pathophysiology is that bisphosphonates and other antiresorptives such as denosumab inhibit osteoclast differentiation and function and increase apoptosis, which all lead to decreased bone resorption and remodeling. The main role of bone remodeling inhibition is further authenticated by a similar prevalence of osteonecrosis of the jaw (ONJ) observed with other anti-resorptive medications such as denosumab. However, to explain the exclusive localization of BRONJ to the jaws, several hypotheses were suggested, such as inhibition of angiogenesis, consistent microtrauma, suppression of immunity, vitamin D deficiency, soft tissue toxicity of bisphosphonate, and inflammation or infection. Among these hypotheses, recent studies have noted that angiogenesis suppression can result in the development of ONJ, and that serum vascular endothelial growth factor (VEGF) level might be a predictive marker of ONJ. Also, bisphosphonates demonstrate anti-angiogenic properties due to their ability to significantly decrease VEGF and
cyclooxigenase COX-2, and the inhibition of VEGF receptor 2 (VEGFR2), causes dysfunction of endothelial cells and reduces arterial remodeling. The modern administration of glucose to wounds of non-diabetic rats leads to inhibition of normal angiogenesis. This treatment decreases angiogenesis through the critical role of high glucose level in diabetes. Also, diabetes is associated with ONJ in rats undergoing alendronate therapy and subjected to tooth extractions. In addition, clinical studies have shown that higher doses of bisphosphonate cause osteonecrosis in patients with diabetes.

Hypercholesterolemia is also known to inhibit angiogenesis by suppressing endothelial function and VEGF expression. There is a relationship between hypercholesterolemia and serum level of VEGF. The endothelial replication necessary for vascular growth is markedly impaired in the presence of hypercholesterolemia. This finding suggests a close correlation between hypercholesterolemia and inhibition of angiogenesis.

In patients with rheumatoid arthritis (RA), bisphosphonates have been predominantly used to inhibit bone loss, especially in patients who develop osteoporosis. This is a common feature in this rheumatic disease. Cyclooxygenase COX-2 inhibitors such as celecoxib are prescribed for arthritic patients due to their mediation of systemic antitumor activity through the inhibition of angiogenesis. Celecoxib suppresses VEGF gene expression both in vitro and in vivo. Vascular endothelial cells express COX-2, and the inhibition of its enzymatic activity by celecoxib prohibits angiogenesis. Treatment with celecoxib was shown to reduce vascularization, lower VEGF level, and induce apoptosis in angiogenic endothelial cells.

Anti-angiogenic agents such as sunitinib, bevacizumab, and sorafenib have been reported to have an association with osteonecrosis. As mentioned above, few studies have been conducted on the correlation of osteonecrosis and COX-2, which is considered to have an influence on VEGF inhibition. Therefore, COX-2 inhibitors are used for diabetes, hypertension, and RA associated with angiogenesis suppression. As a result, these drugs are used to examine the association with ONJ. Since patients with RA suffer a substantial amount of bone loss, anti-resorptive agents like bisphosphonate have been overprescribed to prevent this phenomenon. However, there are few studies related to celecoxib, RA treatment drugs, or the occurrence of ONJ.

The aim of this study was to compare the systemic diseases known to inhibit angiogenesis between patients who were...
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II. Materials and Methods

This retrospective study was conducted with patients who were referred to Wonkwang University Dental Hospital from January 2012 to December 2013 and underwent operations under general anesthesia. This paper was approved by the Institutional Review Board of Wonkwang Dental Research Institute (WKDIRB201409-01).

Based on the medical records, the patients were classified into four groups. Group 1 was patients who were taking bisphosphonate at the first visit, while Group 2 patients did not. Group A comprised patients who were histologically diagnosed with ONJ after the operation, and Group B was patients who were not histologically diagnosed with ONJ after the operation. (Table 1)

At the beginning of the study, the data of all the patients included in Groups 1A, 2A, 1B, and 2B were reviewed. For Group 2B, the authors randomly selected 44 patients who were approximately the same age and had not taken bisphosphonates, anti-resorptive agents such as denosumab or anti-angiogenic agents and were not histologically diagnosed with osteonecrosis. Patients who had been administered intravenous bisphosphonates were excluded from this study.

Since the osteonecrosis incidence and drug potency of intravenous bisphosphonates are different from those of oral bisphosphonates, only intraoral bisphosphonates were studied.19,40 All patients’ medical histories were reviewed with medical records at the first visit, with a focus on hypertension, diabetes mellitus type II (DM), hyperlipidemia, and RA.

To investigate the correlation of hypertension, DM, hyperlipidemia, and RA with the incidence of ONJ in patients taking bisphosphonates, the odds ratio of ONJ was calculated according to the presence of diseases having an influence on inhibition of angiogenesis. For example, to calculate the odds ratio for hypertension, the odds ratios of Group 1A divided by Group 1B in the hypertensive group and in the non-hypertensive group were calculated. The overall odds ratio was then determined by dividing the odds ratio in the hypertensive group by the odds ratio in the non-hypertensive group. To investigate the correlation between these diseases and ONJ in patients who were not taking bisphosphonate, the odds ratio of ONJ was calculated according to the presence of diseases having an influence on inhibition of angiogenesis.

Multivariable logistic regression was used to measure study-specific odds ratios, and Fisher’s exact test determined the association of diseases having an influence on inhibition of angiogenesis with the development of ONJ. All statistical tests were two-sided, and P-values less than 0.05 were considered statistically significant. All analyses were performed using STATA software version 9.1 (StataCorp LP, College Station, TX, USA).

III. Results

Group 1A consisted of 32 patients, Group 1B consisted of 27 patients, Group 2A consisted of 32 patients, and Group 2B consisted of 44 randomly selected patients. (Table 1) A description of the ages and genders of the total study population (total of 135 patients) is shown in Table 2. The median age of all patients was 72 years, and the average oral bisphosphonate dosing period was 41.9±30.8 months.

Comparing the patients who were taking bisphosphonates (Groups 1A and 1B), the history of hypertension had a low odds ratio of 0.55 (P=0.254) in ONJ, with no statistically significant difference. All other variables such as DM, hyperlipidemia, and RA did not show a significant risk in ONJ in the bisphosphonate group compared to the non-bisphosphonate group. Among the patients who were not taking bisphosphonate, only RA was determined to be a risk factor for ONJ. However, the overall odds ratio was not calculated to determine the risk of ONJ due to RA in the non-bisphosphonate group. Therefore, we could not compare the risk of RA in the bisphosphonate group and the non-bisphosphonate group.

Table 1. The classification of patients according to use of bisphosphonate and existence of osteonecrosis of jaw (n=135)

|                        | Taking BPs (Group 1) | Not taking BPs (Group 2) |
|------------------------|----------------------|--------------------------|
|                        | Group 1A (n=32)      | Group 2A (n=32)          |
|                        | Group 1B (n=27)      | Group 2B (n=44)          |
| Histology revealed ONJ |                      |                          |
| Histology did not reveal ONJ |                |

(BPs: bisphosphonates, ONJ: osteonecrosis of the jaw)

1Bisphosphonate-related osteonecrosis of the jaw.

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Table 2. The epidemiological information of the patients

| Age (yr) | Female | Male |
|----------|--------|------|
| <60      | 20     | 0    |
| 60-69    | 32     | 2    |
| 70-79    | 56     | 2    |
| ≥80      | 23     | 0    |

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significant difference between groups. The diseases that were studied did not have any significant relationship with development of BRONJ.

However, the proportion of patients who had no disease influencing the inhibition of angiogenesis was higher in Group 2B compared to the other groups (54.6%; P<0.05). Group 2B patients had an especially low proportion of RA among the diseases having an influence on inhibition of angiogenesis.

Table 3. Proportions and odds ratio of anti-angiogenic diseases in relation to ONJ in the groups of patients taking bisphosphonates

| Anti-angiogenic disease | Group 1A (n=32) | Group 1B (n=27) | Odds ratio | P-value |
|------------------------|----------------|----------------|------------|---------|
| DM                     | Yes (16.8)     | No (50.0)      | 1.26       | 0.616   |
| Hypertension           | Yes (20.6)     | No (21.6)      | 1.15       | 0.683   |
| RA                     | Yes (9.9)      | No (90.6)      | 3.23       | 0.031   |
| Hyperlipidemia         | Yes (9.4)      | No (90.6)      | 3.23       | 0.031   |
| More than 1 disease    | Yes (23.91)    | No (28.25)     | 2.54       | 0.012   |

Table 4. Proportions and odds ratio of anti-angiogenic diseases in relation to ONJ in the groups of patients not taking bisphosphonates

| Anti-angiogenic disease | Group 2A (n=32) | Group 2B (n=44) | Odds ratio | P-value |
|------------------------|----------------|----------------|------------|---------|
| DM                     | Yes (16.8)     | No (50.0)      | 1.46       | 0.548   |
| Hypertension           | Yes (9.9)      | No (90.6)      | 2.11       | 0.114   |
| RA                     | Yes (9.4)      | No (90.6)      | 4.45       | 0.026   |
| Hyperlipidemia         | Yes (9.4)      | No (90.6)      | 1.41       | 0.684   |
| More than 1 disease    | Yes (23.91)    | No (28.25)     | 3.06       | 0.024   |

Table 5. Proportions and odds ratio of anti-angiogenic diseases in relation to ONJ without consideration of bisphosphonates

| Anti-angiogenic disease | Group 1A and 2A (n=64) | Group 1B and 2B (n=71) | Odds ratio | P-value |
|------------------------|------------------------|------------------------|------------|---------|
| DM                     | Yes (18.8)             | No (61.3)              | 1.26       | 0.616   |
| Hypertension           | Yes (30.0)             | No (20.0)              | 3.15       | 0.063   |
| RA                     | Yes (12.5)             | No (87.5)              | 3.23       | 0.094   |
| Hyperlipidemia         | Yes (12.8)             | No (81.3)              | 2.10       | 0.144   |
| More than 1 disease    | Yes (23.4)             | No (26.6)              | 2.54       | 0.012   |
IV. Discussion

There have been attempts to investigate the relationships between BRONJ and concomitant therapies, although associative medication did not exhibit statistically significant results. In those studies, the prevalence of concomitant diseases, such as hypertension, DM, and lung disease, was high but showed no significant relationship with occurrence of BRONJ. This study attempted to focus on systemic diseases that are known to be related to inhibition of angiogenesis and found little significant risk for development of ONJ.

Angiogenesis can be inhibited by four types of diseases: hypertension, DM, RA, and hyperlipidemia. In this study, however, the effects of DM and hypertension were not statistically significant with regard to development of ONJ.

Hypertension appears to be the main cause of endothelial progenitor cell dysfunction. Transplanted or mobilized endothelial progenitor cells are recruited into the foci of neovascularization where they contribute to the re-endothelialization of injured vessels and angiogenesis. In this study, the mean blood pressure of hypertensive patients was low compared to the average blood pressure of 122/79 mmHg. Since most hypertensive patients take medications and maintain low blood pressure, hypertension might have little effect on the development of ONJ.

There is a likelihood of diabetes potentiating osteonecrosis risk during alendronate use. This supposition is supported by bone metabolism changes related to high blood glucose level. In a study using Wistar rats, the incidence of ONJ was significantly greater in the diabetes group. The high frequency of ONJ occurring concomitantly with diabetes has been reported to have several pathophysiology. Diabetes is correlated with microvascular ischemia of the bone, decreased bone turnover and remodeling, endothelial cell dysfunction, and induced apoptosis of osteoblasts and osteocytes. Also, diabetes, which is known to be associated with decrease of VEGF and VEGFR2, causes dysfunction of endothelial cells and reduces arterial remodeling. In 2007, a study attempted to investigate the relationship between BRONJ and diabetes. In the BRONJ patient group, more than half of the patients (58%) had DM or impaired fasting glucose. The proportion of diabetic patients was much higher compared to the proportion of diabetic patients in a control group of patients treated with bisphosphonates and without BRONJ (12%) (P=0.00003). However, there is still no clinical evidence of impaired vascularity under such conditions.

Unlike these studies, DM was not statistically significant with regard to development of ONJ in our study. Since all patients with diabetes mellitus were taking medications and exhibited almost normal glucose level, DM might have little effect on development of ONJ.

The high risk for development of ONJ was higher in the presence of hyperlipidemia and RA. Many patients with RA take bisphosphonates and anti-resorptive drugs that have been reported to be associated with occurrence of ONJ. When patients with RA not taking bisphosphonates were investigated, no patients were prescribed anti-resorptive agents such as denoumab. Instead, most of the patients were taking celecoxib. Studies have shown that celecoxib might have an effect on inhibition of angiogenesis. More studies are necessary to understand whether this effect is due to RA or celecoxib.

To our knowledge, there have been no reports that patients who have hyperlipidemia are at high risk for development of ONJ. However, there is not enough data about the status of disease because of the retrospective design of these studies.

In most reports, the prevalence of ONJ in patients who have used oral bisphosphonates is 1.04 to 1.69 per 100,000 patients per year. In a more recent report, Malden and Lopes derived an incidence of 0.004% (0.4 cases per 10,000 patients per year of exposure to alendronate) from 11 cases of MRONJ reported in a population of 90,000 patients living in southeast Scotland. The prevalence of osteomyelitis of the jaw in patients is 3 to 4 per 100,000 patients per year at the Dutch University Medical Center, which is similar to institutions in the Western world. It is believed that the prevalence of the two diseases has no significant difference. Among the patients who visited the center, the number of elderly patients was found to be high in our hospital. In addition, the patients who were selected for this study were over 60 years in age. Because of these points, the incidence of osteonecrosis seemed to be higher in our patients with systemic diseases.

Patients who had been administered intravenous bisphosphonates were excluded from this study. Intravenous medications are frequently administered to treat malignant diseases such as multiple myeloma, breast cancer, and prostate cancer and are sometimes prescribed simultaneously with anti-cancer chemotherapeutic medications. This means that there is a possibility that the preexistence of diseases such as metastatic tumors or myeloma in the jaw could skew the results of this study. Also, in our study, there was little number of patients who were administered intravenous bisphosphonates.

This study has several limitations that lack consideration.
about the systemic diseases above whether it was adjusted like a normal person through a treatment or not. Since RA can affect the development of ONJ with its anti-angiogenic medications, another experimental study is recommended to show that RA actually contributes to the development of ONJ. In addition, in the groups taking bisphosphonates (Table 3) or not (Table 4), the presence of disease did not affect the development of ONJ. However, the presence of diseases with an influence on inhibition of angiogenesis was found to be significantly correlated with development of ONJ without consideration of bisphosphonates. (Table 5) These results might be due to the small number of patients in this study. We expect further studies on a greater scale to possibly reveal an association of the systemic diseases mentioned in this study with incidence of ONJ.

V. Conclusion

The effects of diabetes and hypertension were not statistically significant on development of ONJ. Patients without diseases having an influence on inhibition of angiogenesis are at less risk for development of ONJ. In addition, patients with hyperlipidemia or RA are at high risk for developing ONJ.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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