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Mi-Ri Lee
Ajou University Dental Hospital
Seung-Il Song
Ajou University Dental Hospital
Jeong-Keun Lee
arcady@ajou.ac.kr

Ajou University Dental Hospital

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Time Course of Healing After Surgery for Medication-Related Osteonecrosis of the Jaw According to the History of Antiresorptive Exposure

Mi-Ri Lee, Seung-Il Song, Jeong-Keun Lee

Department of Oral and Maxillofacial Surgery, Ajou University Dental Hospital, 164 World Cup-ro, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea

Corresponding author: Jeong-Keun Lee

Department of Oral and Maxillofacial Surgery, Ajou University Dental Hospital, 164 World Cup-ro,

Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea

Phone: +82-10-4708-7049;

E-mail: arcady@ajou.ac.kr;

Fax: +82-31-219-5868

Author contributions: Mi-Ri Lee: Conceptualization, Methodology, Data curation, Formal analysis, Visualization, Writing – original draft. **Seung-Il Song:** Investigation, Writing – review & editing. **Jeong-Keun Lee:** Conceptualization, Methodology, Investigation, Supervision, Project administration, Writing – review & editing.

Abstract

Objectives To evaluate time point-specific cumulative probabilities of complete healing after surgery for medication-related osteonecrosis of the jaw (MRONJ) according to the history of antiresorptive exposure.

Materials and Methods In this single-center retrospective cohort, 133 surgically treated patients were classified into the bisphosphonate (BP)-only (n=85), denosumab (Dm)-only (n=34), and sequential BP→Dm (n=14) groups. Treatment failure was considered a competing event, and patients with partial healing were censored at their last assessment. Risk differences (RDs) at 60, 90, and 180 days were estimated using pseudo-observation regression adjusted for age, stage, lesion site, antiresorptive dose, and surgical extent, with Holm correction for six comparisons. Low-dose restriction and bootstrap analyses were performed as sensitivity analyses at 60 days.

Results Complete healing, treatment failure, and partial healing occurred in 96, 17, and 20 patients, respectively. The adjusted Dm−BP difference was +30.3 percentage points at 60 days (95% confidence interval [CI], 9.1–51.4; Holm-adjusted P=0.030), whereas differences at 90 and 180 days were not statistically significant after multiplicity adjustment. The 60-day RD was +27.6 percentage points (95% CI, 4.2–51.1) among low-dose patients, and the bootstrap 95% CI was 9.0–49.8.

Conclusions Dm-only exposure was associated with a higher adjusted cumulative probability of complete healing within 60 days than BP-only exposure. These findings suggest that early postoperative healing may differ according to the history of antiresorptive exposure.

Clinical Relevance Antiresorptive exposure history may be considered when explaining the early course of healing after MRONJ surgery; validation with standardized follow-up is needed before clinical application.

Keywords: medication-related osteonecrosis of the jaw; denosumab; bisphosphonate; antiresorptive therapy; competing risks; postoperative healing

1 Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a serious bone-related complication in patients exposed to antiresorptive agents, such as bisphosphonates (BPs) and denosumab (Dm), and to certain antiangiogenic agents. Management has shifted from prolonged conservative care alone to timely surgical removal of necrotic bone with wound closure, which can achieve high rates of disease resolution and mucosal healing across the MRONJ stages [1–5].

When comparing surgical outcomes according to the type of antiresorptive agent, achievement of healing should be distinguished from the time to healing after surgery. BPs bind to hydroxyapatite and persist in the bone matrix for long periods; therefore, osteoclast suppression may continue after the drug is stopped. Dm directly inhibits receptor activator of nuclear factor-κB ligand but does not accumulate in bone, and its pharmacological effect is more reversible [6,7]. These differences may influence not only long-term healing rates but also the period after surgery in which healing tends to occur.

Cohort studies and a recent meta-analysis have reported various prognostic factors for postoperative healing, including drug dose, stage, and treatment approach [8–10]. Comparisons according to the type of antiresorptive agent have mostly assessed the final status at a single time point or summarized the entire follow-up period. Pautke et al. compared 12-month surgical success among the BP, Dm, and sequential exposure (BP followed by Dm [BP→Dm]) groups [11], and a recent multicenter surgical cohort study of 531 patients evaluated nonhealing during follow-up as a binary outcome [4]. Among studies that analyzed time to healing, Wei et al. used the date of diagnosis as the starting point and included both conservative and surgical treatment in patients with metastatic prostate cancer [12], whereas Park et al. reported a shorter median time to healing after surgery in the Dm group but no significant association with drug type in a Cox model covering the entire follow-up period [13]. Therefore, the time point after surgery at which differences in healing between drug groups become apparent remains unclear. In addition, time point-specific adjusted probabilities of complete healing and absolute between-group differences, with treatment failure before healing treated as a competing event, can describe the course of healing more specifically.

Therefore, in patients who underwent surgery for MRONJ, this study aimed to evaluate the cumulative probability of complete healing at 60, 90, and 180 days after surgery according to the history of antiresorptive exposure, with treatment failure treated as a competing event, and to estimate the absolute

differences between drug groups. Further, we examined the consistency of the drug-group comparison after accounting for the interval from the last dose to surgery.

2 Materials and methods

2.1 Study design and patients

This single-center retrospective cohort study included patients who underwent surgical treatment for MRONJ at the Department of Oral and Maxillofacial Surgery, Ajou University Dental Hospital, between January 1, 2016, and August 31, 2026. Patients were identified based on a review of the operative and electronic medical records, and one index surgery was defined for each patient. Patients with no history of antiresorptive use or an unclear medication history, those who received only a selective estrogen receptor modulator, and those with a history of head and neck radiotherapy were excluded (Fig. 1). The diagnosis of MRONJ and preoperative stage were retrospectively confirmed according to the 2022 position paper of the American Association of Oral and Maxillofacial Surgeons (AAOMS) [1]. This study was approved by the Institutional Review Board of Ajou University Hospital (No. AJOUIRB-DB-2026-511, September 17, 2026), which waived the requirement for written informed consent owing to the retrospective design of the study. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

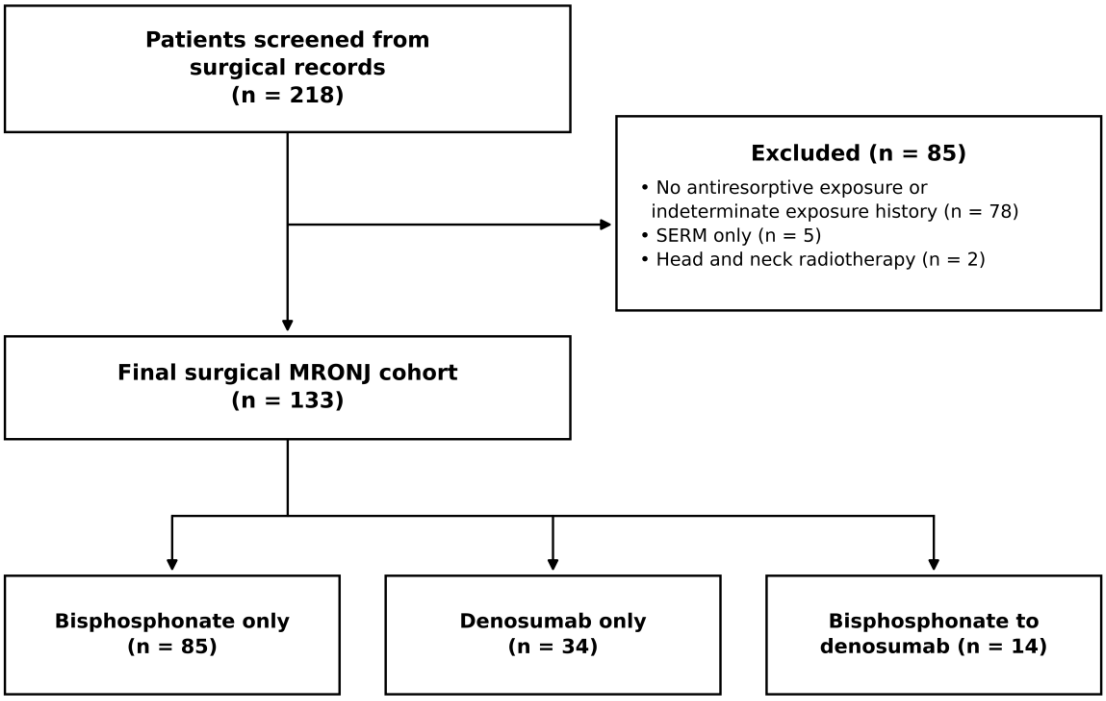

Fig. 1 Study flow diagram

SERM, selective estrogen receptor modulator

2.2 Antiresorptive exposure and clinical variables

Patients were classified into three groups according to the antiresorptive exposure before the index surgery: (1) BP only, (2) Dm only, and (3) BP→Dm.

The baseline characteristics included age, sex, preoperative MRONJ stage, lesion site (maxilla or mandible), and antiresorptive dose (low or high). The surgical extent was classified as less than one-third or at least one-third of the hemi-jaw, based on the procedure name, medical records, and findings on panoramic radiographs and computed tomography images.

The number of days from the date of the last preoperative dose to surgery was defined as the last-dose-to-surgery interval. In the BP→Dm group, the date of administration of the last dose of the most recent antiresorptive agent before surgery was used. For patients whose records contained only the date on which they had been instructed to stop the drug, this date was not substituted for the actual date of the last dose; these patients were included in the main analysis but were excluded from the interval sensitivity analysis.

2.3 Surgical procedure and postoperative care

Depending on the lesion extent, a mucoperiosteal flap was elevated, the sequestra and necrotic or infected bone were removed, and the bone was trimmed with round burs, vulcanite burs, or surgical curettes until viable margins with fresh bleeding were reached. Teeth or implants associated with the lesion were removed when necessary.

The bone defects were thoroughly irrigated with saline and antibiotic solution. Recombinant human bone morphogenetic protein-2 (rhBMP-2) was not used in the eight patients whose surgery was confined to the alveolar bone; in the remaining 125 patients, rhBMP-2 (Novosis®-Dent, CGBIO Co., Ltd., Republic of Korea) was loaded onto a collagen sponge carrier (AteloPlug™, HYUNDAI BIOLAND Co., Ltd., Republic of Korea) and placed in the defect. The wound was closed after hemostasis. Primary closure with mucoperiosteal flap advancement was performed whenever possible. When primary closure was not feasible, the wound was left to heal by secondary intention with local wound care until complete mucosal healing was achieved. In all patients, perioperative antibiotic therapy and follow-up were individualized based on the clinical findings.

The first postoperative visit usually occurred within 1–2 weeks, and visits during early follow-up were scheduled at approximately 1-month intervals. Subsequent intervals were adjusted according to the clinical healing status.

2.4 Definition of postoperative outcomes

Postoperative outcomes were classified as complete healing, partial healing, or treatment failure based on the clinical findings. All outcomes were assessed retrospectively by reviewing the postoperative follow-up findings in the electronic medical records against consistent clinical criteria.

Complete healing was defined as complete clinical mucosal coverage of the surgical site with no residual exposed bone or bone that could be probed through a fistula and no clinical signs of active infection, such as pain, swelling, erythema, purulent discharge, or fistula. When follow-up images were available, the absence of residual sequestrum or active osteolysis at the surgical site was additionally evaluated. The first postoperative visit at which these criteria were met was considered the date of complete healing. The event of interest was the first confirmed complete clinical healing after the index surgery.

Partial healing was defined as clinical improvement from the preoperative status at the last follow-up, without meeting the criteria for either complete healing or treatment failure. This category included patients with a reduction in the extent of exposed bone, progression of soft-tissue healing, or improvement in infection-related symptoms but with residual exposed bone or incomplete mucosal healing. These patients were censored at their last clinical assessment within the study period. At the data cutoff, three patients were still under follow-up, whereas 17 had been lost to follow-up after missing scheduled visits.

Treatment failure was defined as persistent or progressive active MRONJ before complete healing that required additional treatment and was judged, based on the overall follow-up course, to represent failure. Persistence or worsening of purulent discharge, swelling, inflammation, or other signs of active disease was reviewed together with the subsequent treatment, including antimicrobial or other medical therapy, incision and drainage, surgical debridement, or reoperation at the same site. The need for additional medical therapy or a single episode of symptoms alone was not considered failure in patients who had not yet healed. Failure was assigned only when subsequent records confirmed that the findings were persistent or progressive, rather than transient. The competing event date was defined as the date on which clinical findings indicative of failure were first recorded.

2.5 Statistical analysis

The association over the full observation period was summarized using Fine–Gray regression as a supplementary analysis. All adjusted models included age (per 10 years), preoperative MRONJ stage (per one-stage increase), lesion site (reference, maxilla), antiresorptive dose (reference, low dose), and surgical extent (reference, less than one-third of the hemi-jaw), and the Dm-only and BP→Dm groups were compared with the BP-only group. Continuous variables are presented as medians with interquartile ranges (IQRs), and categorical variables as frequencies and percentages. Outpatient follow-up measures according to drug group are presented as descriptive supplementary data (Online Resource 1, Table S1) and were compared using the Kruskal–Wallis test. All analyses were performed using R software (version 4.3.3; R Foundation for Statistical Computing, Vienna, Austria).

2.5.1 Time point-specific probability of complete healing and adjustment for clinical variables

Assessment time points were set at 60, 90, and 180 days after surgery, corresponding to the approximately 2-month, 3-month, and 6-month assessment points used in previous studies on MRONJ surgery [14–18].

The cumulative probability of achieving complete healing by each time point was estimated as the cumulative incidence function (CIF) using the Aalen–Johansen method [19], with complete healing as the event of interest and treatment failure before complete healing as a competing event. Unadjusted CIF curves for each drug group are presented for up to 180 days after surgery along with the time at which the CIF first reached 50% in each group (Fig. 2). Differences between the curves were assessed using Gray's test ($\rho=0$), with administrative censoring at 180 days after surgery [20].

To compare time point-specific cumulative probabilities with adjustments for clinical variables, CIF pseudo-observations were generated at 60, 90, and 180 days from the Aalen–Johansen estimator using a leave-one-out jackknife approach [21]. A separate identity link linear regression model was fitted at each time point, with adjustments for the covariates described above.

The adjusted probabilities of complete healing were standardized according to the covariate distribution in the entire study population, and absolute risk differences (RDs) relative to the BP group are presented with 95% confidence intervals (CIs). Variances were estimated using the HC3 robust estimator. Fig. 3 shows the RDs and 95% CIs at each time point.

2.5.2 Supplementary and sensitivity analyses

To summarize the association between the drug group and complete healing over the full follow-up period as a single estimate, Fine–Gray regression was performed as a supplementary analysis with adjustment for the same covariates as in the time point-specific analysis, and subdistribution hazard ratios (SHRs) with 95% CIs are presented [22].

The overall association with the drug group was assessed using a joint Wald test for two drug contrasts (two degrees of freedom). Details of the estimation procedure are provided in the footnote to Table S2 in Online Resource 1.

Three sensitivity analyses were performed to examine the robustness of the main results (Online Resource 1, Table S3). First, among 123 patients with a recorded last-dose date, the base model and a model that additionally included the last-dose-to-surgery interval were compared at 60, 90, and 180 days. Both models were fitted in the same patients and included the same covariates as the main analysis, and the interval was entered as a log2-transformed continuous variable because of its skewed distribution. Second, the 60-day analysis was restricted to the 121 patients who received low-dose therapy, with antiresorptive dose removed from the covariates. Pseudo-observations were recalculated within these two subsets. Third, a patient-level bootstrap stratified by exposure group (10,000 replicates) was used to obtain a percentile 95% CI for the 60-day RD in all 133 patients; the CIF, all leave-one-out pseudo-observations, and the regression model were re-estimated in each replicate. The low-dose restriction and bootstrap analyses of the 60-day estimate were added post hoc.

2.5.3 Multiple comparisons and interpretation

Holm correction was applied to the six tests in the main analysis, which consisted of two drug contrasts (Dm−BP and BP→Dm−BP) at three time points [23]. Statistical significance for these six comparisons was defined as a Holm-adjusted $P<0.05$. Because the sensitivity analyses were intended to check the consistency of the main results, they were interpreted based on the estimates and 95% CIs without further adjustment for multiple comparisons. The BP→Dm comparison was interpreted as exploratory because of the small sample size and mixed exposure history, but it was included in the six-test family.

3 Results

3.1 Patient characteristics

Among the 133 patients analyzed, 85, 34, and 14 were included in the BP-only, Dm-only, and BP→Dm groups, respectively. The median age was 78.0 years (IQR 72.0–84.0), 125 patients (94.0%) were female, and stage 2 was the most common preoperative stage (106 patients, 79.7%). Low- and high-dose antiresorptive therapy was administered to 121 (91.0%) and 12 (9.0%) patients, respectively. Other baseline characteristics are presented in Table 1. rhBMP-2 was used in 125 patients (94.0%), all except the eight patients whose surgery was confined to the alveolar bone.

Table 1 Baseline characteristics according to antiresorptive exposure group

Characteristic	Total (N=133)	BP (N=85)	Dm (N=34)	BP→Dm (N=14)
Age, years, median (IQR)	78.0 (72.0–84.0)	78.0 (73.0–83.0)	78.0 (69.0–84.0)	81.0 (73.0–84.8)
Sex				
Male	8 (6.0%)	5 (5.9%)	2 (5.9%)	1 (7.1%)
Female	125 (94.0%)	80 (94.1%)	32 (94.1%)	13 (92.9%)
Preoperative AAOMS stage				
Stage 1	22 (16.5%)	11 (12.9%)	8 (23.5%)	3 (21.4%)
Stage 2	106 (79.7%)	72 (84.7%)	23 (67.6%)	11 (78.6%)
Stage 3	5 (3.8%)	2 (2.4%)	3 (8.8%)	0 (0.0%)
Lesion site				
Maxilla	35 (26.3%)	18 (21.2%)	13 (38.2%)	4 (28.6%)
Mandible	98 (73.7%)	67 (78.8%)	21 (61.8%)	10 (71.4%)
Antiresorptive dose				
Low dose	121 (91.0%)	80 (94.1%)	27 (79.4%)	14 (100.0%)
High dose	12 (9.0%)	5 (5.9%)	7 (20.6%)	0 (0.0%)
Related underlying conditions in the low-dose group				
Osteoporosis	112 (84.2%)	74 (87.1%)	26 (76.5%)	12 (85.7%)
Rheumatoid arthritis	11 (8.3%)	6 (7.1%)	1 (2.9%)	4 (28.6%)
Systemic lupus erythematosus	2 (1.5%)	2 (2.4%)	0 (0.0%)	0 (0.0%)
Polymyalgia rheumatica	1 (0.8%)	1 (1.2%)	0 (0.0%)	0 (0.0%)
Treatment indications in the high-dose group				
Breast cancer	6 (4.5%)	2 (2.4%)	4 (11.8%)	0 (0.0%)
Prostate cancer	2 (1.5%)	1 (1.2%)	1 (2.9%)	0 (0.0%)
Multiple myeloma	3 (2.3%)	2 (2.4%)	1 (2.9%)	0 (0.0%)
Other malignancies	1 (0.8%)	0 (0.0%)	1 (2.9%)	0 (0.0%)
Timing of the last antiresorptive dose				
Recorded last-dose date, n	123	75	34	14
Last-dose-to-surgery interval, days, median (IQR)	210.0 (114.5–359.0)	257.0 (102.5–377.0)	207.5 (119.8–311.8)	204.0 (153.0–221.5)
Drug-holiday instruction date only, n	10	10	0	0
Surgical extent				
<1/3 of the hemi-jaw	107 (80.5%)	69 (81.2%)	28 (82.4%)	10 (71.4%)
≥1/3 of the hemi-jaw	26 (19.5%)	16 (18.8%)	6 (17.6%)	4 (28.6%)

Characteristic	Total (N=133)	BP (N=85)	Dm (N=34)	BP→Dm (N=14)
Dental trigger				
Extraction	67 (50.4%)	47 (55.3%)	14 (41.2%)	6 (42.9%)
Implant	9 (6.8%)	6 (7.1%)	3 (8.8%)	0 (0.0%)
Periodontitis	6 (4.5%)	3 (3.5%)	1 (2.9%)	2 (14.3%)
Spontaneous/unknown	51 (38.3%)	29 (34.1%)	16 (47.1%)	6 (42.9%)
rhBMP-2 use	125 (94.0%)	80 (94.1%)	32 (94.1%)	13 (92.9%)

Values are presented as n (%) unless otherwise indicated. Percentages were calculated using the total number of patients in each column as the denominator. Antiresorptive doses and dose-specific conditions are presented in separate blocks. Underlying conditions occasionally overlapped in the low-dose group; therefore, their sum may exceed the number of patients in that group. The last-dose-to-surgery interval is shown for the 123 patients with a recorded last-dose date (BP, 75; Dm, 34; BP→Dm, 14) and excludes the 10 patients for whom only the drug-holiday instruction date was available.

BP, bisphosphonate; Dm, denosumab; BP→Dm, sequential exposure from BP to Dm; IQR, interquartile range; AAOMS, American Association of Oral and Maxillofacial Surgeons; rhBMP-2, recombinant human bone morphogenetic protein-2.

3.2 Cumulative incidence of complete healing and follow-up

During follow-up, complete healing, partial healing, and treatment failure were confirmed in 96, 20, and 17 patients, respectively (Table 2).

Table 2 Distribution of events and censoring according to antiresorptive exposure group

Event / end of observation	Total (N=133)	BP (N=85)	Dm (N=34)	BP→Dm (N=14)
Complete healing	96 (72.2%)	62 (72.9%)	24 (70.6%)	10 (71.4%)
Partial healing	20 (15.0%)	16 (18.8%)	4 (11.8%)	0 (0.0%)
Treatment failure	17 (12.8%)	7 (8.2%)	6 (17.6%)	4 (28.6%)

Complete healing was the event of interest, and treatment failure was considered a competing event. Patients with partial healing were censored at their last clinical assessment. Values are presented as n (%), with the total number of patients in each column as the denominator.

BP, bisphosphonate; Dm, denosumab; BP→Dm, sequential exposure from BP to Dm.

The unadjusted CIFs for complete healing within 180 days after surgery are shown in Fig. 2, and the overall difference among the three curves was not statistically significant (Gray's test, P=0.722). The CIF first reached 50% at 81, 53, and 54 days in the BP, Dm, and BP→Dm groups, respectively. The unadjusted

probability of complete healing within 60 days in the BP, Dm, and BP→Dm groups was 40.6%, 66.1%, and 57.1%, respectively.

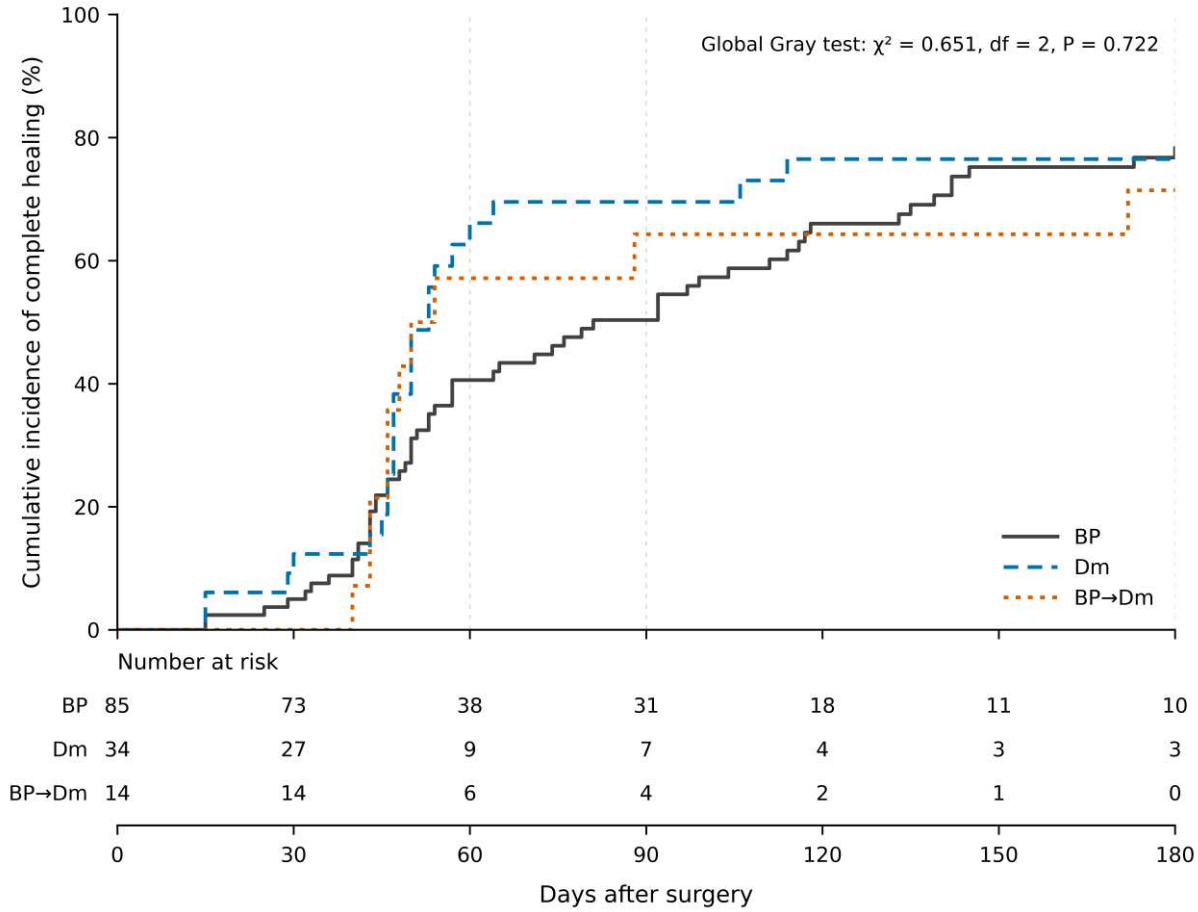

Fig. 2 Unadjusted cumulative incidence of complete healing by antiresorptive exposure group

Estimated using the Aalen–Johansen method, with treatment failure treated as a competing event. Numbers below the plot indicate the patients at risk immediately before each time point.

BP, bisphosphonate; Dm, denosumab; BP→Dm, sequential exposure from BP to Dm

The numbers of events and censored observations by postoperative interval are presented in Online Resource 1, Table S4. Complete healing within 60 days was observed in 31, 20, and 8 patients in the BP, Dm, and BP→Dm groups, respectively, and later complete healing in 31, 4, and 2 patients. Of the 20 patients censored with partial healing, observation ended within 60 days in 15 (BP, 11; Dm, 4).

Outpatient follow-up measures according to drug group are presented in Online Resource 1, Table S1. The median time to the first postoperative visit was 9 days in the BP group and 15 days in the Dm and

BP→Dm groups (P=0.005), whereas the subsequent visit intervals and the confirmation intervals before complete healing did not differ significantly.

3.3 Time point-specific adjusted probability of complete healing

After adjustment for clinical variables, the probabilities of complete healing within 60 days in the BP, Dm, and BP→Dm groups were 39.6%, 69.9%, and 53.3%, respectively. The adjusted probabilities and absolute differences relative to BP at all three time points are shown in Table 3 and Fig. 3.

The adjusted cumulative probability of complete healing within 60 days was higher in the Dm group than in the BP group (RD +30.3 percentage points, 95% CI 9.1–51.4; Holm-adjusted P=0.030). The differences at 90 and 180 days were not statistically significant after Holm correction (Holm-adjusted P=0.125 and 1.000, respectively).

The adjusted differences between the BP→Dm and BP groups at 60, 90, and 180 days were +13.7, +11.5, and −7.6 percentage points, respectively (Table 3).

Table 3 Adjusted cumulative probability of complete healing at 60, 90, and 180 days

Measure	60 days	90 days	180 days
BP, adjusted probability	39.6%	49.5%	77.3%
Dm, adjusted probability	69.9%	72.9%	78.5%
BP→Dm, adjusted probability	53.3%	61.0%	69.6%
Dm−BP RD, pp (95% CI)	+30.3 (+9.1 to +51.4)	+23.4 (+2.9 to +43.8)	+1.2 (−19.4 to +21.8)
Dm−BP Holm P	0.030	0.125	1.000
BP→Dm−BP RD, pp (95% CI)	+13.7 (−20.0 to +47.5)	+11.5 (−21.9 to +44.9)	−7.6 (−41.5 to +26.2)
BP→Dm−BP Holm P	1.000	1.000	1.000

Pseudo-observation linear models were fitted separately at each time point with adjustment for age, preoperative stage, lesion site, antiresorptive dose, and surgical extent. The adjusted probabilities of complete healing were standardized according to the covariate distribution of the entire cohort. The 95% CIs for the RDs were calculated using the HC3 robust variance. Holm-adjusted P values were calculated with the six tests (Dm−BP and BP→Dm−BP at three time points) treated as a single family. The 95% CIs are pointwise and not adjusted for multiplicity.

RD, risk difference; BP, bisphosphonate; Dm, denosumab; BP→Dm, sequential exposure from BP to Dm; CI, confidence interval; pp, percentage points.

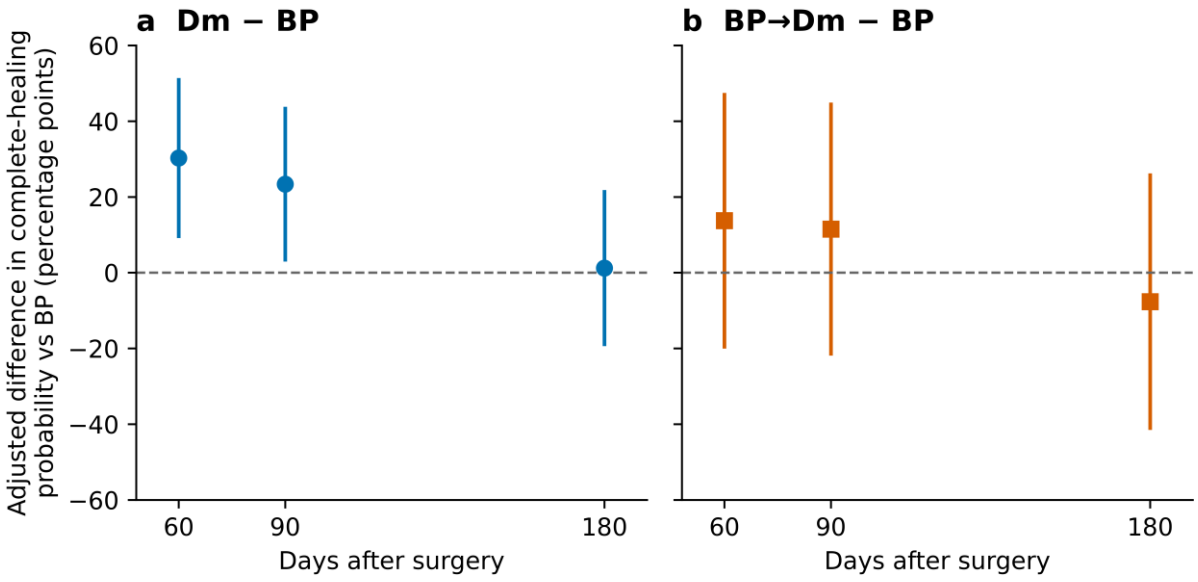

Fig. 3 Adjusted differences in the probability of complete healing at 60, 90, and 180 days after surgery

(a) Dm−BP; (b) BP→Dm−BP

Points indicate absolute RDs adjusted for age, preoperative stage, lesion site, antiresorptive dose, and surgical extent, and error bars indicate 95% CIs based on HC3 robust variance. The horizontal dashed line indicates no difference, and positive values indicate a higher probability of complete healing than in the BP group. Values for each time point were estimated separately, and Holm-adjusted P values for the six comparisons are given in Table 3.

BP, bisphosphonate; Dm, denosumab; BP→Dm, sequential exposure from BP to Dm; RD, risk difference

3.4 Supplementary analysis of the full observation period

In the Fine–Gray model adjusted for clinical variables, the SHR relative to BP was 1.21 (95% CI 0.65–2.26; P=0.549) for the Dm-only group and 0.88 (95% CI 0.38–2.02; P=0.760) for the BP→Dm group. The joint Wald test for the two drug-group coefficients did not show a statistically significant overall association with complete healing (2 degrees of freedom; P=0.793; Online Resource 1, Table S2).

3.5 Sensitivity analyses

Among the 123 patients with a recorded last-dose date, the 60-day Dm−BP difference was +31.5 percentage points (95% CI 10.1–52.8) in the base model and +31.0 percentage points (95% CI 9.4–52.6) in

the interval model, and for both drug contrasts, including those at 90 and 180 days, the estimates changed little after the interval was added.

Among the 121 low-dose patients (BP, 80; Dm, 27; BP→Dm, 14), the 60-day Dm−BP RD was +27.6 percentage points (95% CI 4.2–51.1). The bootstrap 95% CI for the main 60-day RD of +30.3 percentage points in the full cohort was 9.0–49.8 percentage points, similar to the HC3 interval (9.1–51.4 percentage points). All results, including those for the BP→Dm contrast, are presented in Online Resource 1, Table S3.

4 Discussion

In this surgical MRONJ cohort, the 60-day probability of complete healing was 30.3 percentage points higher in the Dm-only group than in the BP-only group, and this difference persisted after Holm correction for all six comparisons. Among 123 patients with a recorded last-dose date, the estimate was similar after additional adjustment for the last-dose-to-surgery interval. In the low-dose restriction analysis, the Dm−BP difference was in the same direction, and the bootstrap CI was similar to the HC3 CI of the main analysis. In contrast, the differences at 90 and 180 days were not significant after multiplicity adjustment, and no significant association with the drug group was observed in the Fine–Gray analysis of the full observation period; however, these findings should not be interpreted as equivalence in later healing or as a loss of drug effect over time. Moreover, the difference in statistical significance between time points does not by itself demonstrate a change in the between-group difference over time.

Our results are broadly consistent with those of previous studies that reported no clear difference in the final healing outcomes between the drug groups. Park et al. reported a shorter median time to healing after surgery in the Dm group; however, the association with drug type was not significant in an adjusted Cox model [13]. Similarly, Kim et al. reported no significant difference in the nonhealing rates according to Dm use in a multicenter cohort of 531 patients [4]. In contrast, Pautke et al. reported that 12-month success after surgery was the lowest in the BP group [11]; however, their analysis was performed at the lesion level, and the final status was assessed at 12 months, unlike the present study. In this study, the full-period SHR (1.21, 95% CI 0.65–2.26) was imprecise, but a difference was observed in the 60-day absolute probability. Time point-specific absolute probabilities should therefore be interpreted together with full-period summary measures,

and numerical comparisons across studies with different patient populations, outcome definitions, and follow-up schedules should be made with caution.

The early differences may be related to the pharmacological differences between the two drugs. BPs bind to bone minerals and remain in the bone matrix for long periods, whereas Dm does not accumulate in the bone, and its inhibition of receptor activator of nuclear factor-κB ligand is reversible with changes in the drug concentration [6,7]. Consequently, the degree of residual suppression of bone resorption may differ between the two drugs, even when the interval from the last dose is the same. Alternatively, if surgery is timed based on the Dm dosing cycle, the observed difference could reflect differences in surgical timing. However, in our cohort, the median last-dose-to-surgery interval in the BP and Dm groups was 257 and 207.5 days, respectively; both exceeded 6 months, and the 60-day difference changed little after further adjustment for this interval (from +31.5 to +31.0 percentage points). Nevertheless, the interval itself also reflects the clinical condition and treatment decisions, and because drug concentrations and bone turnover markers were not measured, we could not establish a causal drug effect or a mechanism involving the recovery of bone remodeling.

Previous studies have reported inconsistent findings regarding drug holidays and healing [24–28]. Some studies have reported that the timing of drug discontinuation was associated with faster symptom resolution or healing [24,25], whereas the benefit of preoperative drug holidays was unclear in surgically treated patients with osteoporosis [26,27] and in patients with cancer receiving high-dose therapy [28]. However, the definitions and starting points of the drug holiday differed between studies, and our interval analysis was intended to evaluate the consistency of the drug-group comparison; therefore, its findings should not be considered evidence of an optimal waiting period before surgery.

Hayashida et al. reported better outcomes after extensive surgery than after conservative surgery among surgically treated patients [29]; therefore, we included surgical extent in the adjusted models. In this study, surgical extent was classified using one-third of the hemi-jaw as the cutoff; thus, it may reflect the size and severity of the underlying lesion as well as the actual extent of resection. Because this variable may also reflect treatment decisions made after exposure, adjustment cannot be assumed to have removed all confounding. In addition, with only 26 patients in the at least one-third group, our ability to evaluate the association of surgical extent itself was limited. rhBMP-2 has been associated with improved postoperative

healing [4,30]; in our cohort, it was used in 94.0% of patients, with similar rates across drug groups (92.9–94.1%). However, all eight patients who did not receive rhBMP-2 underwent surgery confined to the alveolar bone, which made it difficult to separate the contributions of the two factors, and the findings may not be generalizable to settings in which rhBMP-2 is not used routinely.

The BP→Dm group had a mixed exposure history, combining residual BP in the bone matrix with subsequent exposure to Dm. Previous reports of healing in this group have been inconsistent. One study reported a higher 12-month surgical success rate than that in the BP-only group [11], another study found outcomes similar to those in the Dm-only group [31], whereas a prospective multicenter cohort study reported slower healing in patients who had switched from BP to Dm [9]. In this study, the sequential exposure group included only 14 patients, and the CIs were wide at all time points; therefore, these results should be interpreted as exploratory rather than as evidence of an independent drug effect. In addition, all patients in this group received low-dose therapy; therefore, these findings may not apply to patients who switched to high-dose therapy.

This study had some limitations. First, as a single-center retrospective study, it may be subject to bias in patient selection, treatment selection, and outcome ascertainment, and residual confounding due to unmeasured factors, such as the timing of surgery and concomitant medications, cannot be excluded. Second, postoperative follow-ups were not scheduled at fixed intervals for research purposes; therefore, the date of complete healing represents the first visit at which healing was recorded, rather than the actual date of healing, and the exact timing between visits is uncertain. Visit intervals or loss to follow-up related to the healing status may also have influenced the estimates. Third, 94.0% of the patients were female, only 12 received high-dose therapy, and the Dm and BP→Dm groups included only 34 and 14 patients, respectively; therefore, even the 60-day estimates are limited by sample size, and the CIs for later time points and subgroups were wide. Fourth, adjustment for the last-dose-to-surgery interval was possible only in the 123 patients with a recorded last-dose date, and the cumulative dose, treatment duration, and timing of postoperative resumption were not considered. As the pharmacological meaning of the interval differs according to the drug and regimen, additional adjustment cannot be assumed to remove all related confounding. Fifth, only four healing events and four failures were additionally observed in the Dm group after 60 days, which limits the interpretation of the 90- and 180-day estimates, and informative censoring cannot be excluded even though

the proportions of patients censored within 60 days were similar (BP, 12.9%; Dm, 11.8%). In addition, the timing of the first postoperative visit differed between groups, and similar subsequent visit intervals do not imply identical follow-up processes.

5 Conclusions

In this single-center surgical cohort, Dm-only exposure was associated with a higher adjusted cumulative probability of the first complete healing within 60 days after surgery than BP-only exposure. No clear difference between the drug groups was observed at 90 or 180 days or over the full observation period. This association should be validated in further studies with standardized follow-up.

Declarations

Ethics approval

This study was approved by the Institutional Review Board of Ajou University Hospital (No. AJOUIRB-DB-2026-511, September 17, 2026). All procedures were performed in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate

The Institutional Review Board waived the requirement for written informed consent owing to the retrospective design of the study.

Consent to publish

Not applicable.

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Competing interests

The authors declare no conflicts of interest.

Data availability

The data analyzed in this study are not publicly available to protect patient privacy but are available from the corresponding author upon reasonable request.

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