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Comparison of the Effectiveness and Hypocalcemia Risk of Antiresorptive Agents in Patients with Hypercalcemia of Malignancy

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Background: Hypercalcemia of malignancy (HCM), a major metabolic complication of cancer, is often managed with bisphosphonates (BP) and, increasingly, with denosumab. We aimed to compare the effectiveness and safety of denosumab with that of BP, with or without calcitonin, in treating HCM.

Methods: This retrospective cohort study was conducted at a tertiary hospital from 2017 to 2022 and included 317 patients treated for HCM. Participants were divided into three treatment groups: denosumab, intravenous (IV) BP only, and IV BP combined with calcitonin. The primary outcomes measured were changes in calcium levels and the incidence of hypocalcemia. Analysis of covariance was used to adjust for age, sex, body mass index, creatinine level, type of malignancy, and the use of furosemide and steroids.

Results: The mean participant age was 65 years, and 37.5% were female. After adjustment, both denosumab and IV BPs were found to effectively lower calcium levels. Denosumab led to a decrease of 2.0 mg/dL (−15.9%), while IV BP alone resulted in a reduction of 1.8 mg/dL (−13.9%). The largest reduction, of 2.7 mg/dL (−20.9%), occurred with IV BP and calcitonin. Both denosumab and IV BP+calcitonin yielded their lowest calcium levels within 48 hours, whereas the IV BP only group reached a nadir within 72 hours. Despite these differences in treatment effectiveness, hypocalcemia occurred significantly less frequently in the denosumab group compared to the other groups.

Conclusion: Denosumab and IV BP were similarly effective in reducing calcium levels. However, IV BP combined with calcitonin yielded a more rapid and pronounced decrease.

Keywords: Calcitonin; Denosumab; Diphosphonates; Hypercalcemia; Safety; Treatment outcome

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INTRODUCTION

Hypercalcemia of malignancy (HCM) is the most common metabolic complication associated with cancer [1,2]. This condition results from the disruption of calcium homeostasis, often secondary to cancer, and is particularly linked with various forms of the disease, including squamous cell carcinoma and multiple myeloma [1,3-5]. The prevalence of HCM among patients with cancer is reported to be between 2% and 3% [2,6-8]. The seriousness of HCM is underscored by a substantial in-hospital mortality rate of 6% to 8% [9]. Prompt and effective management of HCM is critical not only for improving patient outcomes but also for maintaining quality of life among those affected [1,5]. Timely and effective therapies to manage HCM are essential components of the treatment protocol, with the aims of minimizing morbidity and shortening hospital stays [5].

In the management of HCM, bisphosphonates (BPs) such as pamidronate and zoledronic acid are predominantly utilized [10,11]. In a previous study, a substantial proportion of patients received these agents, with 40.4% treated with pamidronate and 28.7% with zoledronic acid [9]. Secondary agents, namely calcitonin and denosumab, were administered to 27.4% and 0.2% of the patient cohort, respectively [9]. However, the data for that study were collected in 2015, and the relatively low utilization of denosumab is notable [9]. The use of denosumab is expected to increase, given growing recognition of its effectiveness and improved accessibility [5]. From a regulatory standpoint, pamidronate and zoledronic acid are approved for the treatment of HCM, while denosumab has been authorized for use in HCM cases that are refractory to BP therapy in the United States and certain other countries [5].

The recent guidelines of the Endocrine Society represent a meaningful advancement in the clinical approach to HCM, offering a robust framework to substantially improve patient care [12,13]. These guidelines were meticulously developed through systematic review and expert consensus, reflecting the society's commitment to elevating treatment standards. They are particularly commendable for distilling complex clinical decision-making into accessible recommendations. However, all but the first recommendation has been determined to be weak, with very low certainty of evidence [6]. Notably, the literature includes no direct head-to-head studies of antiresorptive agents in patients with HCM. Although a few investigations have been conducted on the effectiveness of BPs or denosumab in preventing HCM among patients with cancer involving bone metastases [14-16], the scarcity of comparative studies on the effectiveness of widely used pharmacotherapies, such as BPs and denosumab, in HCM underscores deficiencies in our clinical understanding.

The study was designed to address the evidentiary gaps identified based on the latest Endocrine Society guidelines. Specifically, a comparative analysis of denosumab versus BPs, with or without the adjunctive use of calcitonin, in a real-world clinical setting appears necessary. Although the retrospective nature of the study introduces certain limitations, it also offers the distinct advantage of reflecting actual clinical practices and patient outcomes. The study objective was to provide a comparative evaluation of denosumab and BPs, the latter both with and without calcitonin. By systematically examining the adjusted effects of these treatments in a real-world clinical context, direct comparative evidence of these agents may be generated, potentially assisting clinicians in managing patients with HCM.

METHODS

Study participants

For this retrospective cohort study, we considered a total of 488 patients admitted with HCM to Seoul National University Bundang Hospital from January 2017 to December 2022. Patients with HCM were defined as those who presented with hypercalcemia at admission and had a cancer diagnosis without other causes of hypercalcemia, such as primary hyperparathyroidism. This assessment was based on electronic health records, which researchers individually reviewed. Of these patients, 171 who did not receive BPs or denosumab during their admission were excluded. Among the remaining 317 patients, 39 received denosumab 120 mg subcutaneously, 122 received intravenous (IV) BPs without calcitonin, and 156 received IV BPs in combination with calcitonin. No patients were treated with both denosumab and calcitonin. Within the IV BP only group, 72 participants (59.0%) received pamidronate, while 50 participants (41.0%) were treated with IV zoledronate. In the group receiving combined IV BP and calcitonin, pamidronate was the more commonly used BP, administered to 121 participants (77.6%), whereas zoledronate was given to 35 (22.4%). Denosumab was administered subcutaneously at a dose of 120 mg. Pamidronate and zoledronate were given via IV doses of 60 or 90 mg and 4 mg, respectively. Calcitonin was administered subcutaneously at a dose of 4 to 8 units/kg for 2 to 3 days. All patients received standard supportive care, including hydration with normal saline.

The Institutional Review Board of Seoul National University Bundang Hospital approved this study (IRB No. B-2407-910-

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101). The requirement for informed consent was waived due to the retrospective nature of the research.

Assessment of anthropometric and biochemical parameters

Standing height and weight were measured without shoes and in light clothing by a trained nurse. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. The use of steroids was defined as the administration of hydrocortisone, prednisolone, methylprednisolone, or dexamethasone during the hospital stay. Similarly, the use of furosemide was defined as the administration of furosemide during admission. Serum calcium, phosphorus, and creatinine levels were measured using an autoanalyzer (TBA-200 FR NEO, Toshiba, Tokyo, Japan). The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Serum parathyroid hormone (PTH) levels were determined via an electrochemiluminescence immunoassay on the Cobas e411 analyzer (Roche Diagnostics, Mannheim, Germany). The baseline calcium level was measured upon admission, and the post-treatment calcium level was defined as the lowest recorded calcium concentration during the hospital stay.

Statistical analysis

Data following a normal distribution are presented as mean±

Table 1. Baseline Characteristics of Participants

Characteristic	Denosumab (n=39)	IV BP only (n=122)	IV BP+calcitonin (n=156)	Total (n=317)	P value
Age, yr	71.9 (58.3–76.4)	64.5 (54.4–71.8)	64.8 (55.8–72.2)	65.0 (55.4–72.8)	0.06
Female sex	20 (51.3)	55 (45.1)	44 (28.2)	119 (37.5)	0.01[c]
BMI, kg/m^2	22.7 (19.9–25.1)	21.8 (18.8–24.4)	20.8 (19.1–23.8)	21.1 (19.1–24.0)	0.09
Calcium, mg/dL	11.0 (10.6–12.2)	11.6 (11.0–12.5)	11.8 (11.3–12.9)	11.6 (11.1–12.8)	<0.01[b,c]
Corrected calcium, mg/dL	11.1 (10.3–12.7)	12.2 (11.2–13.2)	12.6 (11.9–13.8)	12.3 (11.4–13.3)	<0.01[a,b,c]
Phosphorus, mg/dL	3.9 (3.1–4.7)	3.2 (2.7–3.9)	3.0 (2.5–3.8)	3.2 (2.6–3.9)	0.01[a,b]
PTH, pg/mL	5.94±4.90	5.25±1.92	5.12±0.96	5.27±2.20	0.71
Creatinine, mg/dL	0.93 (0.73–1.69)	0.91 (0.64–1.23)	0.98 (0.70–1.40)	0.94 (0.67–1.33)	0.07
eGFR, mL/min	74.6 (37.6–96.3)	83.9 (57.0–122.9)	72.2 (49.8–115.2)	76.5 (51.7–116.2)	0.06
Type of malignancy					<0.01
Lung cancer	6 (15.4)	26 (21.3)	33 (21.2)	65 (20.5)	
Breast cancer	12 (30.8)	16 (13.1)	13 (8.3)	41 (12.9)	
Genitourinary cancer	5 (12.8)	20 (16.4)	10 (6.4)	35 (11.0)	
Head and neck cancer	1 (2.6)	9 (7.4)	23 (14.7)	33 (10.4)	
Hepatocellular carcinoma	0	13 (10.7)	20 (12.8)	33 (10.4)	
Hematologic malignancy	1 (2.6)	17 (13.9)	13 (8.3)	31 (9.8)	
Others	14 (35.9)	21 (17.2)	44 (28.2)	79 (24.9)	
Bone metastasis	1 (2.6)	3 (2.5)	3 (1.9)	7 (2.2)	0.16
Use of furosemide	16 (41.0)	96 (78.7)	151 (96.8)	263 (83.0)	<0.01[a]
Use of steroids	7 (17.9)	67 (54.9)	110 (70.5)	184 (58.0)	<0.01[a]
Type of BP	-				1.00
Pamidronate	0	72 (59.0)	121 (77.6)	193 (69.4)	
Zoledronate	0	50 (41.0)	35 (22.4)	85 (30.6)	
Time to nadir, hr	47.5±9.2	59.8±6.4	39.9±8.8	49.7±8.6	0.01[a,c]
Length of admission, day	7.0 (5.0–17.0)	8.5 (5.0–16.0)	11.0 (8.0–18.0)	10.0 (6.0–17.0)	0.08

Values are expressed as median (interquartile range), number (%), or mean±standard deviation. The groups were compared using analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables.
IV, intravenous; BP, bisphosphonate; BMI, body mass index; PTH, parathyroid hormone; eGFR, estimated glomerular filtration rate.
[a]P<0.05 between denosumab and IV BP only; [b]P<0.05 between denosumab and IV BP+calcitonin; [c]P<0.05 between IV BP only and IV BP+calcitonin.

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standard deviation, while non-normally distributed data are reported as median (interquartile range). Categorical data are expressed as number (percentage). Analysis of variance was utilized to analyze continuous variables, and the chi-square test was employed for categorical variables. Furthermore, analysis of covariance (ANCOVA) was performed with adjustments for age, sex, BMI, creatinine level, type of malignancy, use of furosemide and steroids, and baseline corrected calcium level. The baseline corrected calcium level was additionally adjusted for post-treatment calcium level. *P* values of less than 0.05 were considered to indicate statistical significance. All analyses were conducted using Stata version 13.0 (Stata Corp., College Station, TX, USA) and R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). Graphs were generated using GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA, USA).

RESULTS

Baseline characteristics

The baseline characteristics of participants were assessed based on the treatment received for HCM: denosumab, IV BP only, or IV BP combined with calcitonin (Table 1). The mean age of participants was 65.0 years, with 119 (37.5%) being female. Although not statistically significant, the denosumab group had the oldest participants (median age, 71.9 years), while the IV BP only and IV BP with calcitonin groups had median ages of 64.5 and 64.8 years, respectively ($P=0.06$). Female patients were most prevalent in the denosumab group, at 51.3%, in comparison to 28.2% in the IV BP with calcitonin group ($P=0.01$). BMI was similar across groups, at 21.1 kg/m^2 overall. The initial corrected calcium level was lowest in the denosumab group, at 11.1 mg/dL, with the IV BP only group displaying a level of 12.2 mg/dL. The highest level was observed in the IV BP plus calcitonin group, at 12.6 mg/dL ($P<0.01$). PTH and creatinine levels were similar across groups. Notably, the use of furosemide and steroids varied significantly, with the greatest usage found among patients receiving IV BP with calcitonin ($P<0.01$). Cancer types varied significantly among the groups ($P<0.01$), with lung and breast cancers being the most common. The median length of hospitalization was 10.0 days, without significant differences across groups.

Treatment outcomes

Changes in calcium levels following treatment for HCM are presented in Table 2. The denosumab group exhibited a decrease in the post-treatment corrected calcium level to 9.4 mg/dL, representing a change of −1.1 mg/dL from the baseline. This reduction corresponds to a 10.2% decrease in calcium level ($P<0.01$). In comparison, the group treated with IV BP alone displayed a decrease to 10.1 mg/dL with a change of −1.8 mg/dL, equivalent to a 15.8% reduction ($P<0.01$). The greatest change was observed in the group receiving IV BP in combination with calcitonin, with calcium levels falling to 9.9 mg/dL. This decrease of 2.5 mg/dL represented a 20.0% reduction from baseline levels ($P<0.01$) (Fig. 1).

The adjusted results retained statistical significance, highlighting the robust effects of treatment even after accounting for confounding variables such as age, sex, BMI, creatinine level, type

Table 2. Changes in Calcium Levels Following Treatment for Hypercalcemia of Malignancy

Variable	Denosumab ($n=39$)	IV BP only ($n=122$)	IV BP+calcitonin ($n=156$)	*P* value
Unadjusted				
Post-treatment calcium, mg/dL	9.4 (8.9 to 10.7)	10.1 (9.2 to 11.7)	9.9 (9.2 to 11.0)	0.07
Change in calcium, mg/dL	−1.1 (−2.3 to −0.8)	−1.8 (−3.1 to −0.7)	−2.5 (−3.7 to −1.8)	<0.01[b]
Change in calcium, %	−10.2 (−19.5 to −7.3)	−15.8 (−25.0 to −5.6)	−20.0 (−27.2 to −14.5)	<0.01[a,b]
Adjusted				
Post-treatment calcium, mg/dL	10.2 (9.6 to 10.8)	10.6 (10.3 to 10.9)	10.0 (9.7 to 10.3)	<0.01[b]
Change in calcium, mg/dL	−2.0 (−2.7 to −1.3)	−1.8 (−2.1 to −1.5)	−2.7 (−3.1 to −2.5)	<0.01[b]
Change in calcium, %	−15.9 (−20.8 to −11.0)	−13.9 (−16.3 to −11.5)	−20.9 (−23.2 to −18.8)	<0.01[b]

Values are expressed as median (interquartile range). Variables were compared between groups using analysis of variance (ANOVA). Analysis of covariance (ANCOVA) was performed with adjustments for age, sex, body mass index, creatinine level, type of malignancy, and the use of furosemide and steroids. The baseline corrected calcium level was additionally adjusted for post-treatment calcium level.
IV, intravenous; BP, bisphosphonate.
[a]$P<0.05$ between denosumab and IV BP+calcitonin; [b]$P<0.05$ between IV BP only and IV BP+calcitonin.

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of malignancy, and the use of furosemide and steroids. The denosumab group exhibited a 15.9% reduction in calcium level, while the IV BP only group experienced a 13.9% decrease. The group receiving IV BP in combination with calcitonin displayed the greatest reduction (20.9%), a statistically significant finding ($P<0.01$).

Fig. 2 depicts the changes in calcium levels over time. For denosumab, the nadir was attained at 47.5±9.2 hours of admission (Table 1, Fig. 2). With IV BP alone, the nadir occurred at 59.8±6.4 hours. In contrast, the combination of IV BP and calcitonin achieved a nadir earlier, at 39.9±8.8 hours, which is similar to the timing observed in the denosumab group but with a more pronounced decrease. Thus, the addition of calcitonin to BP therapy may both accelerate and amplify the reduction of calcium levels compared to BP treatment alone.

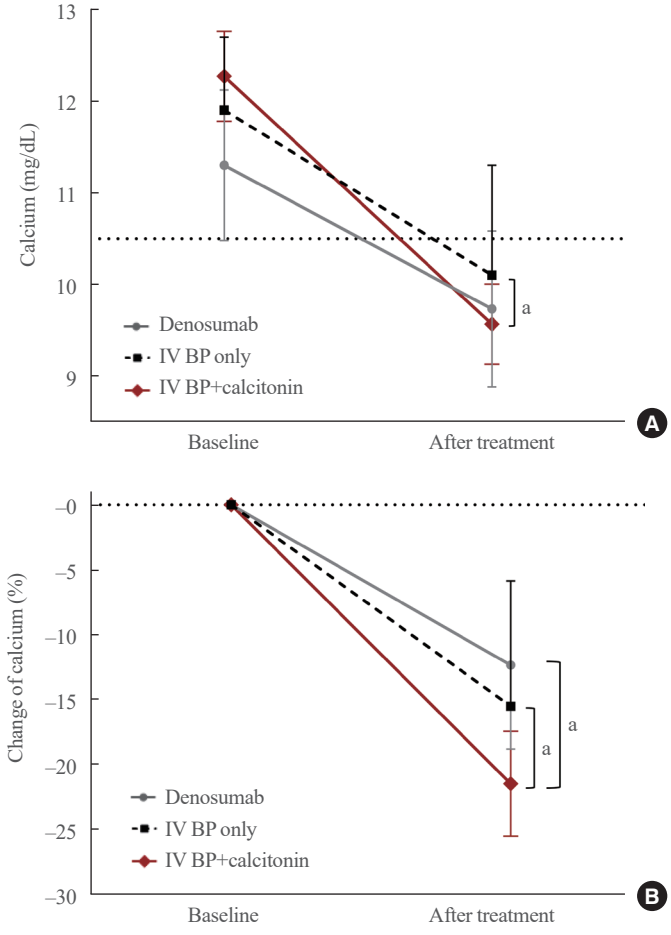

Fig. 1. (A) Absolute and (B) percentage changes in calcium levels by treatment for hypercalcemia of malignancy. IV, intravenous; BP, bisphosphonate. [a]$P<0.05$ between groups.

Post-treatment calcium status

Table 3, Fig. 3 summarizes the nadir calcium levels following the three treatments for HCM: denosumab, IV BP only, and IV BP with calcitonin. Hypocalcemia was less common in the denosumab group (2.6%) than among those receiving IV BP alone (14.8%). In comparison, 5.1% of patients in the IV BP+calcitonin group experienced hypocalcemia. Statistically significant differences were observed between the IV BP only group and both the denosumab and the IV BP with calcitonin groups (both $P=0.01$). However, the rates of normocalcemia and persistent hypercalcemia were similar across groups ($P=0.29$ and $P=0.71$, respectively).

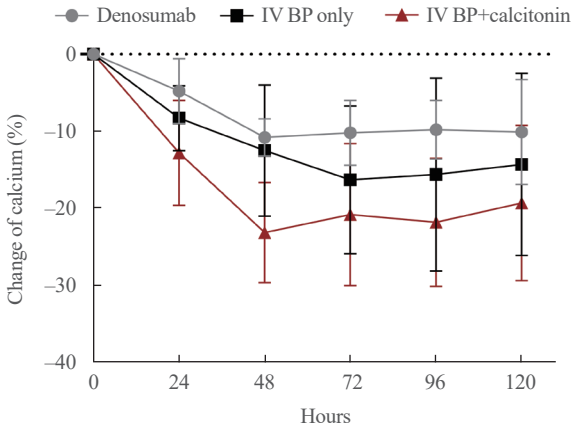

Fig. 2. Changes in calcium levels over time following treatment for hypercalcemia of malignancy. IV, intravenous; BP, bisphosphonate.

Table 3. Calcium Status Following Treatment for Hypercalcemia of Malignancy

Variable	Denosumab ($n=39$)	IV BP only ($n=122$)	IV BP+calcitonin ($n=156$)	Total ($n=317$)	P value
Hypocalcemia	1 (2.6)	18 (14.8)	8 (5.1)	27 (8.5)	0.01[a,b]
Normocalcemia	24 (61.5)	58 (47.5)	83 (53.2)	165 (52.1)	0.29
Hypercalcemia	14 (35.9)	46 (37.7)	65 (41.7)	125 (39.4)	0.71

Values are expressed as number (%). The variables were compared between groups using the chi-square test.
IV, intravenous; BP, bisphosphonate.
[a]$P<0.05$ between denosumab and IV BP only; [b]$P<0.05$ between IV BP only and IV BP+calcitonin.

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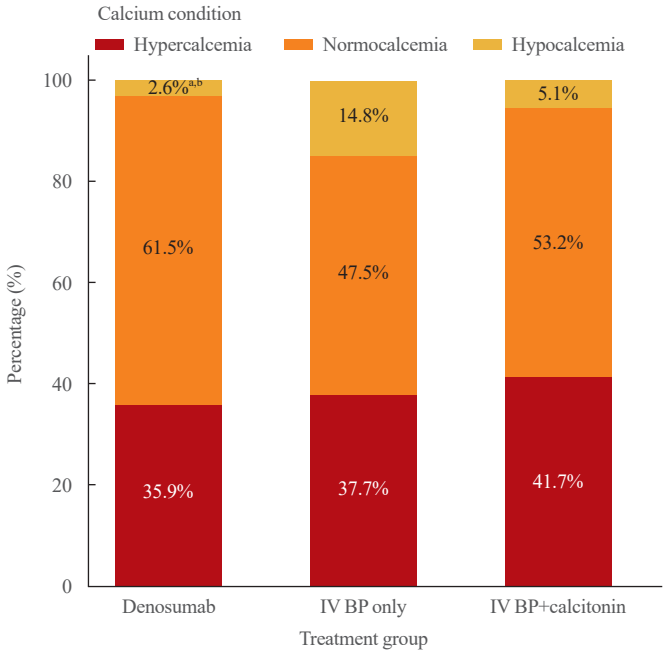

Fig. 3. Calcium status following treatment for hypercalcemia of malignancy. Data are presented as percentages. IV, intravenous; BP, bisphosphonate. [a]$P<0.05$ between denosumab and IV BP only; [b]$P<0.05$ between denosumab and IV BP+calcitonin.

Subgroup analysis by BP type

Table 4 details the changes in calcium levels after treatment. Patients treated exclusively with IV pamidronate experienced a decrease of 2.0 mg/dL, equating to a 15.4% reduction. For those receiving only IV zoledronate, the decrease was 1.6 mg/dL, corresponding to an 11.9% reduction. No significant difference was observed in the impact on calcium levels between the IV pamidronate-only and IV zoledronate-only groups, and these effects were comparable to those observed with denosumab (Table 4, Fig. 4). A subgroup analysis based on the dose of pamidronate (60 mg vs. 90 mg) indicated similar reductions in calcium levels (Supplemental Table S1).

However, a notable difference emerged with combination treatments. Specifically, the subgroup receiving IV pamidronate combined with calcitonin experienced a decrease in calcium levels of 2.4 mg/dL (−18.7%), while those treated with IV zoledronate combined with calcitonin experienced a more pronounced reduction of 3.9 mg/dL (−28.4%). This suggests that the combination of IV zoledronate with calcitonin leads to a greater reduction in calcium levels than the combination of IV pamidronate with calcitonin ($P<0.01$). Additionally, the drop in calcium levels in the group receiving IV zoledronate and calcitonin was significantly larger than that found in patients treated with IV zole-

Table 4. Subgroup Analysis of Changes in Calcium Levels by Treatment Regimen

Variable	Denosumab ($n=39$)	IV Pam only ($n=72$)	IV Zol only ($n=50$)	IV Pam+calcitonin ($n=121$)	IV Zol+calcitonin ($n=35$)	*P* value
Unadjusted						
Post-treatment calcium, mg/dL	9.4 (8.9 to 10.7)	10.1 (9.2 to 11.4)	10.1 (9.1 to 12.2)	10.1 (9.4 to 11.0)	9.7 (8.6 to 11.2)	0.096
Change in calcium, mg/dL	−1.1 (−2.3 to −0.8)	−1.9 (−3.2 to −0.8)	−1.5 (−3.0 to 0.0)	−2.4 (−3.2 to −1.7)	−3.7 (−5.4 to −2.2)	<0.01[b,c,d,f,g]
Change in calcium, %	−10.2 (−19.5 to −7.3)	−17.2 (−24.8 to −7.2)	−11.4 (−25.0 to 0.0)	−19.7 (−25.1 to −13.7)	−26.5 (−37.4 to −16.9)	<0.01[c,d,e,f,g]
Adjusted						
Post-treatment calcium, mg/dL	10.1 (9.5 to 10.7)	10.5 (10.1 to 10.9)	10.9 (10.4 to 11.3)	10.2 (9.9 to 10.5)	9.3 (8.7 to 9.9)	<0.01[a,c,f]
Change in calcium, mg/dL	−2.2 (−2.8 to −1.5)	−2.0 (−2.4 to −1.6)	−1.6 (−2.1 to −1.1)	−2.4 (−2.8 to −2.0)	−3.9 (−4.2 to −3.7)	<0.01[c,f,g]
Change in calcium, %	−16.8 (−21.7 to −11.9)	−15.4 (−18.5 to −12.3)	−11.9 (−15.8 to −8.1)	−18.7 (−21.2 to −16.1)	−28.4 (−32.7 to −23.8)	<0.01[c,e,f,g]

Values are expressed as median (interquartile range). All calcium levels were calculated as corrected levels. The groups were compared using analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. Analysis of covariance (ANCOVA) was performed with adjustments for age, sex, body mass index, creatinine level, type of malignancy, and the use of furosemide and steroids. The baseline corrected calcium level was additionally adjusted for post-treatment calcium level.
IV, intravenous; Pam, pamidronate; Zol, zoledronate.
[a]$P<0.05$ between denosumab and IV Zol only; [b]$P<0.05$ between denosumab and IV Pam+calcitonin; [c]$P<0.05$ between denosumab and IV Zol+calcitonin; [d]$P<0.05$ between IV Pam only and IV Zol only; [e]$P<0.05$ between IV Pam only and IV Pam+calcitonin; [f]$P<0.05$ between IV Zol only and IV Zol+calcitonin; [g]$P<0.05$ between IV Pam+calcitonin and IV Zol+calcitonin.

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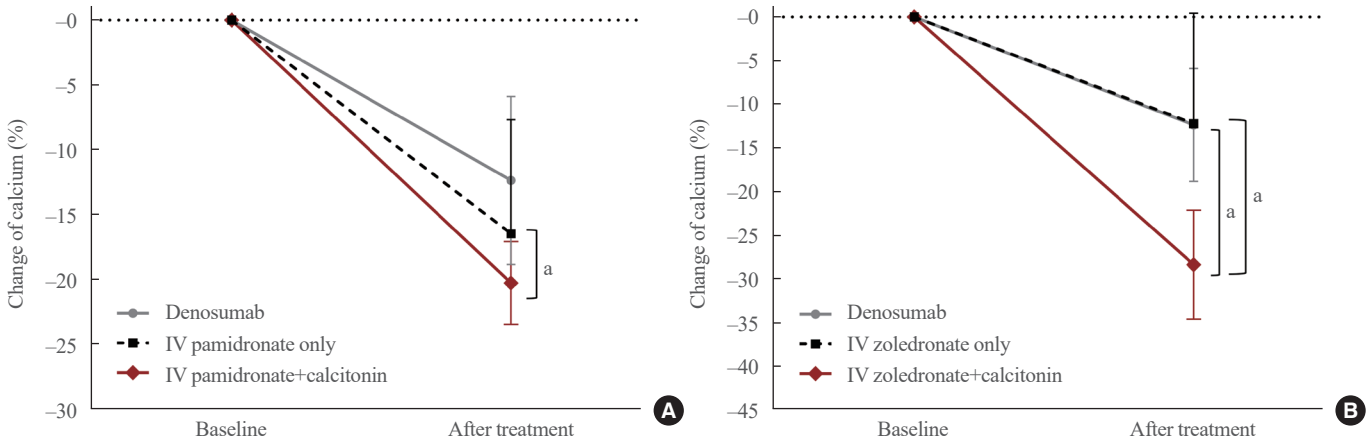

Fig. 4. Changes in calcium levels by type of bisphosphonate: (A) pamidronate and (B) zoledronate. IV, intravenous. [a]$P<0.05$ between groups.

Table 5. Subgroup Analysis of Calcium Status by Treatment Regimen

Variable	Denosumab ($n=39$)	IV Pam only ($n=72$)	IV Zol only ($n=50$)	IV Pam+calcitonin ($n=121$)	IV Zol+calcitonin ($n=35$)	*P* value
Hypocalcemia	1 (2.6)	7 (9.7)	11 (22.0)	3 (2.5)	5 (14.3)	0.01[a,b]
Normocalcemia	24 (61.5)	34 (47.2)	24 (48.0)	70 (57.9)	13 (37.1)	0.13
Hypercalcemia	14 (35.9)	31 (43.1)	15 (30.0)	48 (39.7)	17 (48.6)	0.45

Values are expressed as number (%). The groups were compared using the chi-square test for categorical variables.
IV, intravenous; Pam, pamidronate; Zol, zoledronate.
[a]$P<0.05$ between denosumab and IV Zol only; [b]$P<0.05$ between denosumab and IV Zol+calcitonin.

Table 6. Pre- and Post-Treatment Renal Function by Treatment Regimen

Variable	Denosumab ($n=39$)	IV Pam only ($n=72$)	IV Zol only ($n=50$)	IV Pam+calcitonin ($n=121$)	IV Zol+calcitonin ($n=35$)
Pre-treatment creatinine, mg/dL	0.93 (0.73–1.69)	1.04 (0.70–1.31)	0.70 (0.57–0.98)	0.99 (0.72–1.40)	0.93 (0.67–1.25)
Post-treatment creatinine, mg/dL	0.86 (0.68–1.56)	0.85 (0.72–1.25)	0.72 (0.55–1.09)	0.86 (0.60–1.29)	0.89 (0.57–1.23)
P value	0.866	0.481	0.246	0.083	0.091

Values are expressed as median (interquartile range). The paired *t* test was performed in all groups.
IV, intravenous; Pam, pamidronate; Zol, zoledronate.

dronate alone ($P<0.01$).

The incidence of hypocalcemia also differed significantly among the groups: 2.6% of patients in the denosumab group experienced hypocalcemia, compared to 22.0% in the IV zoledronate-only group and 14.3% of those receiving IV zoledronate combined with calcitonin (Table 5). Both the achievement of normocalcemia and the persistence of hypercalcemia displayed similar rates across groups ($P=0.13$ and $P=0.45$, respectively). Additionally, renal function was comparable before and after treatment in all treatment groups (Table 6).

DISCUSSION

In this study, we conducted a retrospective analysis of patients with HCM, focusing on the effectiveness of antiresorptive agents such as denosumab and BPs, with or without the addition of calcitonin. Our findings indicated that both a standard dose of denosumab and IV BPs alone effectively reduced calcium levels. However, denosumab treatment produced a faster decrease. Furthermore, the combination of IV BPs with calcitonin resulted in the most rapid and pronounced reduction in calcium lev-

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els. The rate of post-treatment hypocalcemia was lowest in the group treated with denosumab, although persistent hypercalcemia was similarly prevalent across groups. These findings suggest that denosumab may represent a safe and fast-acting treatment for HCM, while the addition of calcitonin to BP treatment may offer an advantage in safety and effectiveness over the use of BPs alone.

In the present study, reductions in calcium levels were similar between denosumab and IV BPs. However, patients treated with denosumab were less likely to remain hypercalcemic than those who received IV BPs, and the nadir calcium level was achieved earlier with denosumab. Notably, no placebo-controlled trials involving denosumab have been reported in the context of HCM. Ethical concerns arise from the established effectiveness of BPs; conducting a trial in which patients receive a placebo instead of a known effective treatment is problematic. Furthermore, no randomized controlled studies have compared denosumab with BPs in patients with HCM. However, a retrospective study of patients with multiple myeloma reported that IV BP and denosumab led to similar proportions of patients achieving normocalcemia after treatment [17]. Indirect comparisons have also been drawn regarding the recurrence risk of HCM between denosumab and BPs [14,16]. Combined data from two randomized trials showed that denosumab was more effective than zoledronic acid in reducing the risk of HCM, doing so by 37% during the follow-up period [7]. Furthermore, another randomized study comparing denosumab with zoledronic acid in patients with breast cancer and bone metastases reported that denosumab was superior to zoledronic acid in preventing skeletal-related events, including HCM, which had rates of 1.7% and 3.5%, respectively [16]. This partially aligns with our finding that patients were less likely to remain hypercalcemic if treated with denosumab rather than with zoledronic acid (28% vs. 38%, respectively) [16]. Differences in the antiresorptive mechanisms of these medications [18] could be responsible for the differing responses, with denosumab exhibiting more potent activity in suppressing bone resorption. Although the results of the previous retrospective study focused solely on multiple myeloma [17] and the described trial data involved only patients with bone metastases [14,16] (hence, varied outcomes are expected), the stronger antiresorptive properties of denosumab could potentially reduce treatment failure rates more effectively than BPs, as recommended in the recent Endocrine Society guidelines [12]. Nonetheless, further research is required to support these findings and refine treatment protocols for HCM.

In the present study, the combination of calcitonin with BP therapy led to a more rapid and pronounced decrease in calcium levels compared to denosumab or BP alone. Notably, this greater reduction may be due in part to the selection of patients with higher initial calcium levels for calcitonin treatment. Nevertheless, the robustness of the analysis was upheld even after adjusting for baseline calcium levels, indicating a genuine additive effect of calcitonin to BP treatment. This combination is particularly effective due to calcitonin's rapid but transient action in lowering calcium levels, which complements the more sustained effects of BPs that inhibit bone resorption [19,20]. A recent report, consistent with our findings, indicated that IV BP with calcitonin yielded a greater decrease in calcium levels than BP therapy alone [21]. However, the initial serum calcium levels in the group receiving combination therapy were higher than those in the BP only group, and the post-treatment calcium levels were comparable. This could stem from the fact that all patients in the combination therapy group were treated with pamidronate, while 26% of the BP only group received zoledronate, potentially resulting in a less pronounced reduction in calcium levels in the combination group [21]. In contrast, our study included a statistically similar proportion of patients receiving zoledronate in both treatment groups, possibly contributing to more definitive results. Thus, these findings may serve as evidence supporting the integration of calcitonin with BPs in the management of severe hypercalcemia, aligning with recent Endocrine Society guidelines [12].

Regarding BP type, while both medications significantly reduced calcium levels, zoledronate demonstrated a more potent antiresorptive effect than pamidronate. This finding aligns with the established higher potency of zoledronate for antiresorptive activity, which may contribute to its superior effectiveness in reducing calcium levels [22]. These results align with a previous pooled analysis of trials, which found that zoledronic acid was more effective than pamidronate in the treatment of HCM [15]. The more potent and longer-lasting effects of zoledronate may be preferred in cases for which a rapid and sustained reduction in calcium levels is desired.

The study has several strengths. It utilized real-world data, providing insights into actual clinical practices and outcomes. This approach improved the generalizability and applicability of the study findings to routine clinical settings. Additionally, the study featured a large sample size of 317 patients, bolstering the statistical power and reliability of the results. Another key strength of this study is the direct comparison between various treatment regimens: denosumab, BP alone, and BPs combined with calcitonin. Such a comparative analysis is essential for de-

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termining relative effectiveness and safety, thus providing clear, actionable information for clinical decision-making. The use of ANCOVA to adjust for potential confounding variables such as age, sex, BMI, creatinine level, type of malignancy, and the use of furosemide and steroids minimized the likelihood that the treatment effects were biased by these factors. This analytical method strengthened the credibility and accuracy of the results. Furthermore, we did not limit our examination to the primary outcome of calcium level reduction; we also investigated the incidence of hypocalcemia and persistent hypercalcemia. This assessment may contribute to a more thorough understanding of the safety and effectiveness profiles of the treatments.

This study also has several limitations. Given its retrospective design, differences between patient groups may have influenced the outcomes, despite efforts to adjust for known confounders. Consequently, the observed effect of IV BP with calcitonin might have been influenced by high baseline calcium levels, even though adjustments were made. Additionally, the single-center nature of the study may limit the generalizability of the results to other clinical settings or populations, as the treatment dose and frequency were not stratified. The inclusion of patients with hypercalcemia of both humoral and bone metastatic origins may also contribute to variability in treatment response, complicating the ability to discern treatment effectiveness across these distinct pathologies. The absence of data on vitamin D levels, which can meaningfully impact calcium dynamics, and the potential for residual confounding by differences in baseline calcium levels or underlying disease states—even after adjustment—could also have biased the results. These factors underscore the need for cautious interpretation of the comparative effectiveness of denosumab versus BPs in managing HCM. Furthermore, calcium levels were monitored only during the hospitalization period, potentially hindering the accurate evaluation of hypocalcemia incidence and the precise assessment of hypercalcemia management.

In conclusion, this study may provide insights into the effectiveness of the standard dose of denosumab and BPs in treating HCM. Both denosumab and IV BPs were independently effective in reducing calcium levels in the management of HCM. The standard dose of denosumab and IV BP were similarly effective at lowering calcium levels, with denosumab achieving the nadir calcium level more rapidly than IV BP treatment. As anticipated, the addition of calcitonin to BP therapy led to a more pronounced decrease in calcium levels. Thus, this combination may offer a superior therapeutic strategy, especially in cases requiring a greater reduction in calcium levels. Overall, this research contributes to ongoing discussion regarding optimal treatment for HCM, underscoring the necessity for personalized treatment plans in accordance with current guidelines. It also highlights the need for further research to refine these treatment strategies.

CONFLICTS OF INTEREST

Jung Hee Kim is a deputy editor of the journal. But she was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

Conception or design: S.H.K. Acquisition, analysis, or interpretation of data: S.H.K. Drafting the work or revising: S.H.K., S.S.P., J.H.K., S.W.K., S.H.K., J.H.K., C.S.S. Final approval of the manuscript: S.H.K., S.S.P., J.H.K., S.W.K., S.H.K., J.H.K., C.S.S.

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