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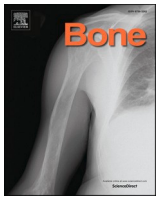

Full Length Article

Tolerability of the first infusion of once-yearly zoledronic acid within one to two weeks after hip fracture surgery

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ABSTRACT

Objective: Once-yearly infusions of zoledronic acid (ZA) 5 mg may be optimal for secondary fracture prevention after hip fracture (HF), but there are crucial side effects of ZA. This study assessed the tolerability of the first infusion of once-yearly ZA within one to two weeks after HF surgery and to identify risk factors for acute-phase reactions (APRs) and the decrease in serum calcium (Ca) concentration.

Methods: We analyzed 84 patients (average age: 83 years, 18 men and 66 women) who met the inclusion criteria. The patients underwent the first infusion of ZA one to two weeks after HF surgery and received antipyretic analgesics and active vitamin D analog.

Results: APRs occurred in ten patients (11.9%) and all these patients had pyrexia (>37.5 °C) and/or other symptoms. The asymptomatic hypocalcemia (serum Ca < 8.3 mg/dL) incidence was 6.0% at 7 days after ZA infusion. Compared with female patients without APRs, female patients with APRs had significantly higher levels of serum 25-dihydroxyvitamin D at baseline and serum C-reactive protein on the day ZA was administered (day 0). Multiple linear regression analyses showed that serum level of tartrate-resistant acid phosphatase-5b were significantly associated with an absolute decrease in serum corrected Ca from day 0 to day 7.

Conclusions: The first infusion of ZA within one to two weeks after HF surgery was well tolerated with the combined use of antipyretic analgesics and active vitamin D analog. Higher inflammatory condition after surgery which is more likely sensitized by ZA administration may increase the risk of APRs, and high bone turnover may increase hypocalcemia risk.

1. Introduction

Osteoporosis has become a major public health concern worldwide, with the increase in the number of elderly people [1]. Among osteoporotic fractures, hip fracture (HF) has the greatest impact on morbidity and mortality and results in a notable increase in medical and nursing care costs [2–4]. Patients with a history of HF have the highest risk of subsequent fractures, especially within 2 years after a fracture [4–7]. These patients should be preferentially offered assessment for the initiation of pharmacologic therapy for osteoporosis, and precautions should be taken against subsequent fractures [2–4].

Bisphosphonates (BPs) reduce the risk of fracture in older patients with a history of HF [8–11]. The initiation of oral BPs (alendronate and risedronate) has been strongly recommended as the first-line anti-osteoporosis therapy for patients who have undergone HF surgery [4]. Currently, oral BPs are commonly used, but a study showed that patients initiating oral therapies, including oral BPs, exhibited poorer persistence and compliance than those initiating injectable therapies [12].

Intravenous zoledronic acid (ZA) infusion once-yearly has been recommended as a useful first-line option for patients who have difficulty with oral BPs (e.g., bed-bound elderly and patients with dysphagia or cognitive impairment) [4]. ZA has the strongest affinity for hydroxyapatite and has inhibitory effects on osteoclasts [13]. In a randomized controlled trial, ZA therapy significantly reduced new clinical fractures by 35% and mortality by 28% in patients who had experienced HF [9]. ZA could serve as an optimal agent to prevent secondary prevention after HF. However, the American Society for Bone and Mineral Research (ASBMR) Task Force Report does not recommend intravenous and subcutaneous pharmacologic agents including ZA within the first 2 weeks after HF surgery because of two main reasons: 1) hypocalcemia

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associated with vitamin D deficiency and perioperative overhydration, and 2) acute-phase reactions (APRs) of flu-like symptoms after ZA infusion [4]. Distinguishing infections such as surgical site infection and APRs is difficult [4]. Although there are several concerns such as APRs and hypocalcemia, ZA infusion during hospitalization within the first 2 weeks after HF surgery has many advantages as follows: earlier initiation of antiosteoporosis therapy for secondary fracture prevention, quick response to each adverse effect, and securing space and time during ZA infusion. No study has investigated whether ZA infusion within the first 2 weeks after HF surgery is associated with notable adverse effects in fragile HF patients. Moreover, it is unclear if ZA infusion within the first 2 weeks is harmful.

This study aimed to 1) precisely investigate the incidence of APRs and hypocalcemia and evaluate tolerability of the first infusion of ZA within one to two weeks after HF surgery, and 2) identify risk factors for the occurrence of APRs and for the decrease in serum calcium (Ca) concentration.

2. Methods

2.1. Study design and participants

This study was an open-label, single-center, observational study involving patients who received the first intravenous infusion of once-yearly ZA 5 mg during hospitalization after hip repair. Consecutive patients who underwent HF surgery were recruited between March 2018 and February 2020 at our hospital and were followed up until discharge. HF was diagnosed in cases with low-energy trauma such as a fall on the ground. In our protocol, all patients who met the study criteria were treated with ZA (Reclast; Aasahi Kasei Pharma Co. Ltd., Tokyo, Japan) 5 mg infusion within one to two weeks after HF surgery. ZA was administered over at least 30 min at 10:00 on day 0, and patients were observed for 7 days (Fig. 1). During the investigation period, all patients were started on daily supplementation with oral active vitamin D analog (alfacalcidol or eldecalcitol) after admission. Patients who had not taken oral active vitamin D analog or had taken cholecalciferol before admission were started taking alfacalcidol 0.5 μg/day. For patients who had already received oral active vitamin D analog before admission, they continued the same dose of alfacalcidol or eldecalcitol. All patients started taking antipyretic analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen as postoperative pain medication just after HF surgery and continued for 2 weeks after surgery. The study was conducted in accordance with the Declaration of Helsinki and with the approval of the ethical review boards of our institution. All patients in the study provided written informed consent.

2.2. Inclusion and exclusion criteria

Patients who underwent HF surgery were eligible for the study, regardless of having taken antiosteoporosis agents except ZA. The exclusion criteria were as follows: patients with other diseases with unstable physical status such as advanced-stage cancer, patients who refused to receive ZA, patients who received ZA in the past, and patients with contraindications to ZA. Moreover, patients with hypocalcemia (serum corrected Ca (cCa) level of <8.3 mg/dL [2.075 mmol/L]) before HF surgery were excluded from the study. Patients with severe renal disorders [creatinine clearance (CCr) of <35 mL/min calculated by the Cockcroft and Gault formula: CCr [mL/min] = (140 − age) × body weight (kg) × [0.85, if female] / 72 × serum creatinine (mg/dL)] were also excluded from the study. No patient enrolled in this study had pathological HFs with primary bone tumors, metastatic bone tumors, myeloma, myelitis, or metabolic bone diseases such as osteomalacia and hyperparathyroidism.

2.3. Clinical assessments

At recruitment, age, sex, height, weight, and body mass index (BMI) were recorded for all study participants. Medical history including osteoporotic fracture history and the presence or absence of pharmacologic therapy for osteoporosis was assessed. We evaluated each patient regarding the presence of cognitive impairment or mental illness such as depression, walking capability before injury, and history of conditions that affect walking capability (leg paralysis caused by cerebrovascular or spinal disorders and leg surgery such as total knee or hip arthroplasty and fracture repair).

In this study, APR was defined as an influenza-like illness and/or pyrexia starting within 3 days following ZA infusion in accordance with previous studies [14–16]. The presence or absence of nasopharyngitis, arthralgia, myalgia, headache, malaise, chills, and other symptoms starting within 3 days following ZA infusion were examined by one

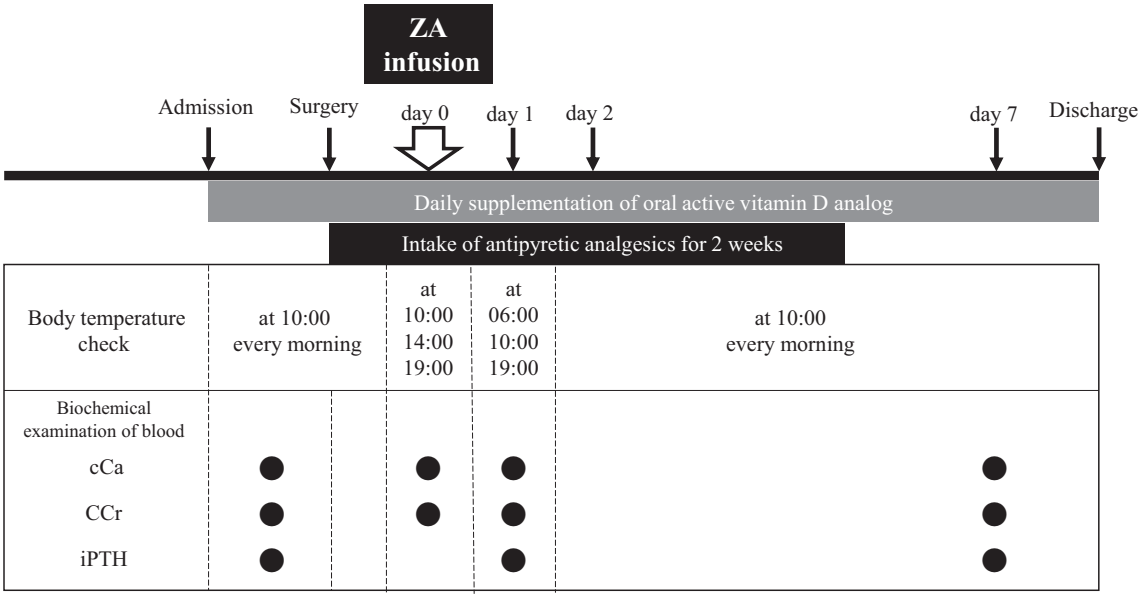


Fig. 1. Study design and schedule.
cCa serum corrected calcium, CCr Creatine clearance, iPTH serum intact parathyroid hormone, ZA zoledronic acid.

observer (M.K.) everyday within 7 days after ZA infusion. Body temperature was recorded by medical staff at 10:00 every morning during hospitalization (Fig. 1). Body temperature at baseline was set as the average body temperature of 3 days before ZA infusion. Body temperature was recorded at 10:00, 14:00, and 19:00 on day 0, at 6:00, 10:00, and 19:00 on day 1, and at 10:00 every morning from day 2 to 7 under antipyretic analgesics (Fig. 1). Pyrexia after ZA infusion was defined as an increase in body temperature from baseline of ≥1 °C in addition to a body temperature of ≥37.5 °C [15,16]. If a patient had pyrexia, body temperature was continuously measured every 3 to 4 h until the body temperature decreased to the baseline value. NSAIDs or acetaminophen were given for all patients for 2 weeks after surgery including the period before and after ZA infusion (Fig. 1). The type and dose of antipyretic analgesics were determined by reference to CCr (oral acetaminophen 900–1500 mg daily for patients with CCr 35–50, oral loxoprofen 120-180 mg daily for patients with CCr 50<).

2.4. Biochemical examination of blood

Blood samples were collected in the morning after an overnight fast, and routine serum chemistry tests were performed using standard automated techniques. The levels of serum albumin (Alb), creatinine (Cr), C-reactive protein (CRP), and Ca were measured on the day before surgery and on day 0, 1, and 7 after ZA infusion (Fig. 1). Serum Ca levels were corrected for Alb using the following formula: cCa = [total Ca + (4.0 − Alb)] × 0.8, where Alb <4.0 g/dL. The normal range of serum cCa was 8.3–10.3 mg/dL [2.075–2.585 mmol/L] in our laboratory, and hypocalcemia was defined as serum cCa < 8.3 mg/dL [2.075 mmol/L] according to a previous study [17]. CCr was calculated using the previously described formula. The incidence of laboratory hypocalcemia by grade was classified according to the Common Terminology Criteria for Adverse Events version 5.0. Acute kidney injury after ZA infusion was defined as any of the following: 1) increase in serum Cr > 0.3 mg/dL on day 1 or 2) increase in serum Cr on day 7 > 1.5 times compared with the value on day 0, according to the modified Kidney Disease Improving Global Outcomes criteria [18]. Serum intact parathyroid hormone (iPTH) was measured by electrochemiluminescence immunoassay (Roche Diagnostics, Tokyo, Japan) on the day before surgery, day 0, and day 7 after ZA infusion. Serum 25-dihydroxyvitamin D [25(OH)D] was measured by electrochemiluminescence immunoassay (Roche Diagnostics) before surgery. Tartrate-resistant acid phosphatase 5b (TRACP-5b) was measured by enzyme immunoassay (Osteolinks TRAP-5b; SB Bioscience Co. Ltd., Tokyo, Japan) before surgery.

2.5. Radiological assessment

Frontal and lateral whole-spine radiographs were obtained before ZA infusion. The presence or absence of vertebral deformity in the coronal and sagittal planes occurring subsequent to vertebral fractures was also assessed. Bone mineral density (BMD) values were measured by dual energy X-ray absorptiometry (DXA) (Horizon W; Hologic, Inc., Marlborough, MA, USA) before ZA infusion. Areal BMD of the lumbar spine (L1–4) and the femoral neck in the opposite non-implanted side was assessed by DXA. A BMD T-score was calculated for all measured sites.

Plain hip radiographs were reviewed 12 months postoperatively, and hip fracture healing was evaluated using plain radiographs in patients who underwent internal fixation.

2.6. Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous valuables are expressed as means or means ± standard deviation (SD). Two-sided *p*-values <0.05 were considered statistically significant. Statistical analysis of comparisons between groups was performed using the Mann–Whitney *U* test, chi-square test, and Fisher exact test. Changes in paired data were analyzed using the Wilcoxon signed-rank test. The associations are expressed as the results of the Pearson correlation test. Linear regression models were used to determine the influence of independent variables in order to explain the absolute decrease in cCa from day 0 to day 7 after the first ZA infusion (ΔCa_{0-7d}). To assess the predictors of ΔCa_{0-7d}, multiple regression analysis with forward stepwise selection was performed with thresholds of $\alpha = 0.10$ and $\alpha = 0.05$ for entry and retention, respectively. The explanatory variables included items examined in the study (age, sex, BMI, active vitamin D analog supplementation period, previous treatment for osteoporosis, BMD T-score of the lumbar spine and femoral neck, and biochemical data at baseline [cCa, iPTH, 25 (OH)D, and TRACP−5b]). We removed multicollinearity in multivariable logistic regression analysis; when there were two variables with a Spearman correlation coefficient of >0.7, we eliminated one variable. All statistical analyses were performed using JMP software (version 12.2.0; SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Baseline characteristics

From 131 consecutive patients who underwent HF surgery, 84 patients (64.1%) were enrolled in our study (Fig. 2). Thirty-six patients with CCr < 35 mL/min, six patients who refused ZA infusion, three patients with unstable physical status due to advanced-stage cancer, one patient who had already received ZA, and 1 patient with primary hyperparathyroidism were excluded (Fig. 2).

Table 1 shows the characteristics of the 84 patients who underwent the first intravenous infusion of ZA after HF surgery (66 women and 18 men; mean age at HF surgery, 82.8 years). Seventy percent of the 84 patients needed assistance in walking before their injury, and 25% of them lived in nursing facilities. Thirty-seven percent of all patients had a history of leg paralysis or leg surgery. Furthermore, 37 patients (44%) were diagnosed with cognitive impairment or depression. Rates of pharmacological therapy for osteoporosis was notably low (9%), although 61 patients (73%) had a history of prevalent osteoporotic fracture, and the BMD T-score in the femoral neck area was markedly low (average T-score; −3.8).

3.2. Adverse events after the first ZA infusion within one to two weeks after HF surgery

Ten patients (all female; mean age, 82.6 years) had pyrexia after ZA infusion and were treated with intravenous fluid infusion during hospitalization. Three patients complained of headache and malaise, 1 patient complained of a headache, and 1 patient complained of myalgia and arthralgia. The remaining 5 patients had only pyrexia. In all ten patients, their symptoms occurred within 12–24 h after infusion and completely disappeared within 72 h. All patients with symptoms had both negative blood and urine cultures and negative flu test results. Chest radiography or contrast computed tomography did not reveal any sources of pyrexia in the lung, and there were no signs of infection in the surgical wounds. After a serial examination, all patients with symptoms were diagnosed with APRs, and the incidence rate of APR was 11.9%.

All patients started daily supplementation with active vitamin D analog after admission, and the mean administration period before ZA infusion was 12.8 days. Seventy-three patients (87%) started taking alfacalcidol (mean dose; 0.53 μg/day) before ZA infusion (mean administration period: 12.6 days). The mean serum cCa level (mg/dL) was 9.34 ± 0.43 before starting active vitamin D analog, 9.74 ± 0.42 just before ZA infusion (day 0), and 9.42 ± 0.43 and 9.21 ± 0.44 on day 1 and day 7, respectively (Fig. 3a). Serum cCa level significantly increased after starting active vitamin D analog supplementation ($p < 0.001$). Serum cCa level rapidly and significantly decreased after ZA infusion (day 0 vs day 1: $p < 0.001$, day 0 vs day 7: $p < 0.001$, day 1 vs day 7: $p < 0.001$). Although none of these patients exhibited symptomatic

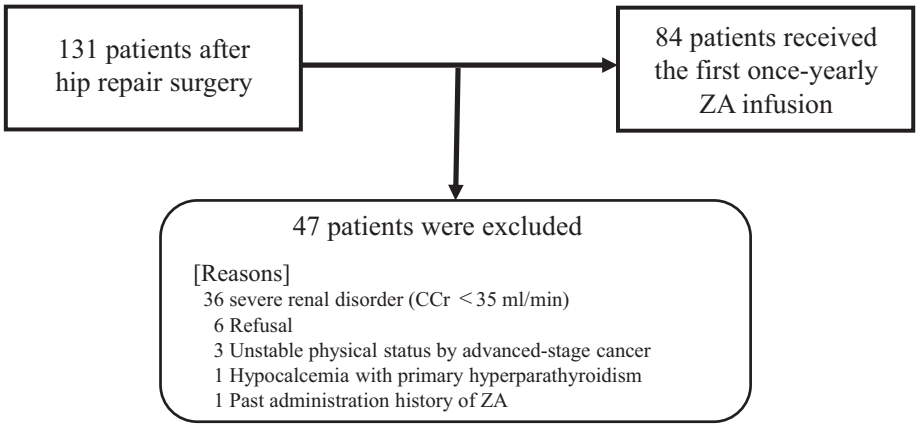


Fig. 2. Study flowchart and disposition of subjects.
CCr Creatine clearance, ZA zoledronic acid.

Table 1
Characteristics of patients receiving once-yearly ZA infusion after HF surgery.

Characteristics ($n = 84$)	
Age (yr)	82.8 ± 6.3
Gender (male:female)	18 (21%):66 (79%)
BMI (kg/m^2)	20.9 ± 3.6
Residence (home:nursing facilities)	63 (75%):21 (25%)
Walking capability before HF surgery	
Without aid	25 (30%)
With aid (stick, senior's cart, handrail)	48 (57%)
Wheel chair	11 (13%)
Presence of history which affects walking capability	31 (37%)
Presence of cognitive impairment or mental illness	37 (44%)
Presence of prevalent osteoporotic fracture	61 (73%)
Presence of prevalent HF	4 (5%)
Presence of pharmacologic therapy for osteoporosis	
Naive	76 (90%)
Oral bisphosphonate	7 (8%)
Denosumab	1 (1%)
LS BMD T-score	−2.4 ± 1.5
FN BMD T-score	−3.8 ± 1.1
Serum cCa (mg/dL)	9.34 ± 0.43
CCr (ml/min)	54.5 ± 19.7
iPTH (pg/mL)	43.4 ± 19.5
TRACP-5b (mU/dL)	440 ± 308
25 (OH) D (ng/mL)	10.5 ± 5.1
Interval between surgery and ZA infusion (days)	11.0 ± 2.6
Active vitamin D analog supplementation after admission (dose [μg/day], administration period before ZA infusion [days])	
Alfacalcidol ($n = 73$)	0.53 ± 0.14, 12.6 ± 4.3
Eldecalcitol ($n = 11$)	0.64 ± 0.13, 15.8 ± 3.9

Values are shown as mean ± SD.
BMD Bone mineral density, *BMI* Body mass index, *cCa* Corrected calcium, *CCr* Creatine clearance, *FN* femoral neck, *LS* lumbar spine, i*PTH* intact parathyroid hormone, *TRACP-5b* tartrate-resistant acid phosphatase 5b, *ZA* zoledronic acid, *25(OH)D* 25-hydroxycholecalciferol.

hypocalcemia during the study, grade 1 hypocalcemia, defined as <8.3 mg/dL [2.075 mmol/L], was observed in 1 patient (1.2%) on day 1 and in 5 patients (6.0%) on day 7. Thirteen patients (15.5%) had serum cCa < 8.8 mg/dL [2.2 mmol/L] on day 7 and the return of serum cCa level to baseline level was subsequently confirmed in 9 of the 13 patients. The mean serum iPTH levels (pg/mL) was 43.9 ± 19.4 at baseline, 46.0 ± 18.8 on day 0, and 83.0 ± 64.5 on day 7. Serum iPTH level rapidly and significantly increased after ZA infusion (baseline vs day 0: $p = 0.70$, baseline vs day 7: $p < 0.001$, day 0 vs day 7: $p < 0.001$) (Fig. 3b).

Mean CCr was maintained before and after infusion (day 0: 55.6 ± 18.6, day 1: 55.3 ± 18.6, day 7: 54.6 ± 18.4), but 6 patients (7.1%) had CCr < 35 mL/min on day 7. No patients met the criteria for acute kidney injury during the investigation period.

The effect for fracture healing after ZA infusion could be evaluated in 59 patients (70%) 12 months postoperatively. Thirty-nine internal fixations and 20 hemiarthroplasties were performed. There were no patients with delayed union or pseudoarthrosis in these 39 patients.

3.3. Risk factors for APRs within one to two weeks after HF surgery

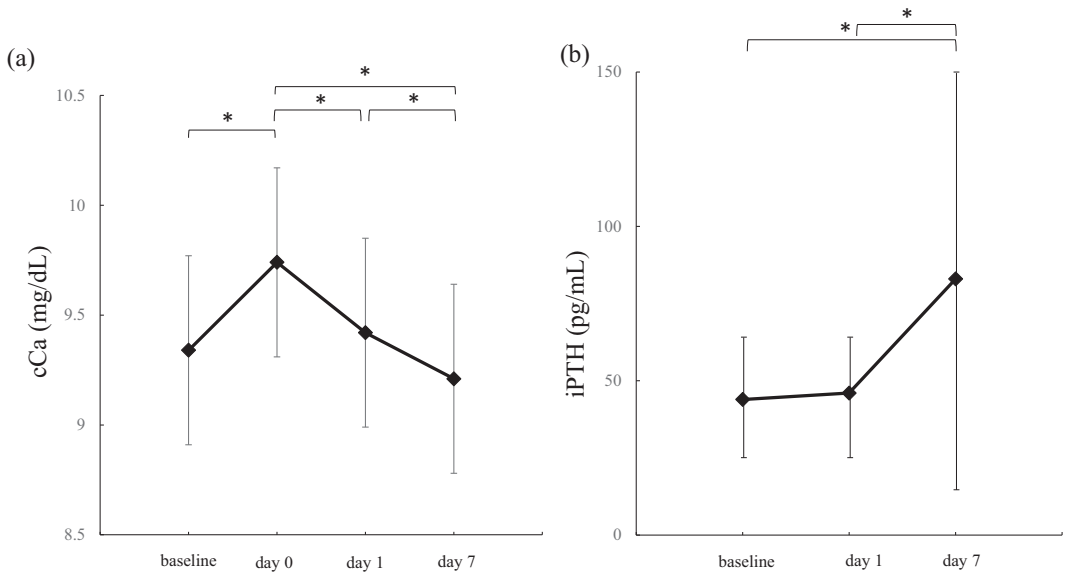
To identify risk factors for the occurrence of APRs, patients were divided into two groups (group with APR [$n = 10$] and group without APR [$n = 74$]). Univariate analysis of the APR+ and APR− groups revealed that the serum CRP level on day 0 was significantly higher in the APR+ group (APR+: 3.78 ± 3.59; APR−: 1.57 ± 1.55; $p = 0.043$). The serum level of 25(OH)D at baseline was significantly higher in the APR+ group (APR+: 14.6 ± 5.5; APR-: 10.0 ± 4.9; $p = 0.016$). No male patients had APRs in this study. Results of the univariate analysis of the APR+ and APR- groups are shown in Table 2, with the female patients divided into two subgroups (APR+ [n = 10], APR− [$n = 56$]). The serum level of 25(OH)D at baseline was significantly higher in the APR+ group ($p = 0.024$). The serum level of CRP on day 0 was significantly higher in the APR+ group ($p = 0.023$).

3.4. Risk factors for decreased serum cCa within one to two weeks after HF surgery

The decrease in cCa from day 0 to day 7 after the first ZA infusion (ΔCa_{0-7d}) had a significant positive correlation with log TRACP-5b ($r = -0.358$, $p = 0.003$) and a significant negative correlation with previous treatment for osteoporosis ($r = 0.262$, $p = 0.03$) (Table 3). After we used stepwise methods for the multivariate analysis, one explanatory variable had notably high statistical significance: log TRACP-5b. The results of the multiple regression analysis using four explanatory variables (age, sex, BMI, log TRACP-5b) revealed that log TRACP-5b ($\beta = -0.466$, $p = 0.007$) was significantly and independently associated with ΔCa_{0-7d}.

4. Discussion

To our knowledge, this is the first study to investigate the tolerability of the first ZA infusion within one to two weeks after HF surgery. This study revealed that the first infusion of ZA was well tolerated under the combined use of antipyretic analgesics and active vitamin D analog. Higher inflammatory condition after HF surgery which is more likely sensitized by ZA administration may increase the risk of APRs, and high



< 8.3mg/dL	0%	1.2%	6.0%
< 8.8mg/dL	0%	3.6%	15.5%

Fig. 3. Time-course changes of serum (a) cCa and (b) iPTH level after the first intravenous infusion of ZA.
Data are presented as mean ± SD, *$p < 0.01$.
CCr Creatine clearance, iPTH serum intact parathyroid hormone, ZA zoledronic acid.

bone turnover may increase the risk of hypocalcemia.

Intravenous and subcutaneous pharmacologic agents were administered as the therapeutic options after the first 2 weeks of the perioperative period, and one of the concerns within the first 2 weeks of the perioperative period is APR, particularly in patients without pretreatment with BPs [4]. Reid et al. investigated adverse events in 7765 postmenopausal women with osteoporosis, and reported the APRs occurred in 42% of the ZA administration group [14]. APRs were more common in non-Japanese Asians, younger subjects, and NSAIDS users and were less common in smokers, patients with diabetes, previous users of oral BPs, and Latin Americans [14]. Shiraki et al. assessed the incidence of APRs in Japanese patients with primary osteoporosis and reported that APRs after the first infusion occurred in 51.2% (169/330) of the ZA administration group [19]. Comparison of baseline factors showed APRs were less common with a higher neutrophil/lymphocyte ratio, lower serum levels of procollagen type I N-terminal propeptide, older age, and higher percentage of pretreatment with BPs. Similarly, Takada et al. reported the APRs occurred in 17.4% (32/184) after the first ZA administration in real clinical practice, and odds ratios (OR) of the significant factors involved in the development of APRs were significantly smaller for patients aged >80 years (OR 0.23, vs. age ≤69 years) and for the switching cases who had continuously received other BPs until ZA administration (OR 0.12, vs. those who had not taken other BPs for more than 2 years before ZA administration or had never received BPs) [20].

Simple comparisons cannot be made because of differences in the patients' background, longer ZA infusion time, and the presence of the combined use of antipyretic analgesics and active vitamin D analog. However, the incidence of APRs in this study was considerably lower than in previous studies [17,20,21], although the rate of pretreatment for osteoporosis including BPs was low (9%). This is explained by the significant contribution of older age, longer infusion time, and usage of antipyretic analgesics including NSAIDS to the occurrence of APRs. Several studies suggest the difference in immune responses is associated with the occurrence of APRs. Previous studies reported that amino-BPs inhibit farnesyl pyrophosphate synthase (FPPS), and increasing the production of isopentenyl pyrophosphate by inhibiting FPPS stimulates the immunological system, leading to the release of inflammatory cytokines from peripheral blood γδ T cells [22–24]. It is unclear why APRs are more common in younger patients, but it could be inferred that stronger reaction to amino-BPs occurred because of the younger age.

In this study, patients received ZA for longer infusion time (>30 min) during hospitalization instead of 15 min employed in the two HORIZON FDA registration trials [9,17]. AKI was not seen in this study as that has been associated with an infusion period of less than 15 min, and longer infusion time may be associated with the lower incidence of APRs. ZA given as an infusion of 45–60 min is recommended from the aspect of safety [25].

Furthermore, the lower incidence of APRs was attributed to the suppression of inflammatory responses or because the patients' conditions made inflammatory response difficult. Wark et al. reported that administration of acetaminophen/paracetamol or ibuprofen for 3 days just after ZA administration significantly lowered the incidence of temperature increases by half and reduced the incidence of the symptoms [15]. Okimoto et al. reported that the incidence of ZA-induced APRs was decreased by about 30% with loxoprofen administration [16]. In this study, all patients started NSAIDS or acetaminophen paracetamol after HF surgery and continued during the period before and after ZA infusion. The lower incidence of APRs in this study can be explained by the use of antipyretic analgesics. A high serum CRP level before ZA administration was identified as a significant risk factor for APR in our study. Generally, serum CRP increases after HF repair surgery and decreases to the normal range about 2 weeks after surgery. Dicounzo et al. revealed that ZA administration induces a transient increase in tumor necrosis factor-α and interleukin-6, and these cytokines were higher in APR+ patients [26]. They suggested that these cytokines are involved in fever pathogenesis [26]. In fact, serum CRP on day 1 was higher than on day 0 in this study (data not shown). Our finding suggests that patients with higher inflammatory condition after HF surgery are more likely sensitized by stimuli induced by ZA administration. It may be safe to postpone ZA administration if patients show higher CRP levels after HF surgery.

A high serum level of 25(OH)D at baseline was also identified as a significant risk factor for APR in this study. The relationship between

Table 2
Univariate analysis of characteristics of female patients receiving ZA infusion: with APR versus without APR.

Characteristic	APR (+) [n = 10]	APR (−) [n = 56]	*p* value
Age (yr)	82.6 ± 5.6	83.5 ± 5.9	0.66
BMI (kg/m^2)	20.2 ± 3.0	20.9 ± 3.7	0.55
Presence of cognitive impairment or mental illness	6 (60.0%)	24 (42.8%)	0.36
Presence of pharmacologic therapy for osteoporosis	3 (30.0%)	14 (25.0%)	0.79
Interval between surgery and ZA infusion (days)	11.3 ± 0.7	11.2 ± 3.2	0.91
Active vitamin D analog supplementation period before ZA infusion [days]	15.1 ± 4.5	13.0 ± 4.4	0.18
Antipyretic analgesics administration period before ZA infusion [days]	10.9 ± 4.7	11.9 ± 3.9	0.46
Body temperature at baseline	36.8 ± 0.22	36.7 ± 0.37	0.55
LS BMD T-score	−2.8 ± 1.1	−2.6 ± 1.4	0.75
FN BMD T-score	−4.1 ± 1.2	−4.0 ± 1.0	0.82
Serum cCa on day 0 (mg/dL)	9.90 ± 0.26	9.73 ± 0.43	0.24
Serum creatine on day 0 (mg/dL)	0.63 ± 0.13	0.61 ± 0.14	0.68
CCr on day 0 (ml/min)	49.0 ± 11.8	53.9 ± 17.7	0.40
WBC on day 0 (×10^3/μL)	7.14 ± 2.79	6.35 ± 1.91	0.68
CRP on day 0 (mg/dL)	3.78 ± 3.59	1.34 ± 1.31	0.023*
iPTH (pg/mL)	39.0 ± 12.0	44.6 ± 20.5	0.41
TRACP-5b (mU/dL)	493 ± 331	394 ± 235	0.32
25 (OH) D (ng/mL)	14.6 ± 5.5	10.1 ± 5.3	0.024*

Values are shown as mean ± SD.
$p < 0.05$ was considered a statistically significant difference (*$p < 0.05$).
BMD Bone mineral density, *BMI* Body mass index, *cCa* Corrected calcium, *CCr* Creatine clearance, *CRP* C-reactive protein, *FN* femoral neck, i*PTH* intact parathyroid hormone, *LS* lumbar spine, *NSAIDs* Non-steroidal anti-inflammatory drugs, *TRACP-5b* tartrate-resistant acid phosphatase 5b, *WBC* white blood cell, *ZA* zoledronic acid, *25(OH)D* 25-hydroxycholecalciferol.

Table 3
Regression coefficients for $\Delta Ca_{0\text{-}7d}$ versus other parameters.

	Correlation coefficient (*r*) vs $\Delta Ca_{0\text{-}7d}$	*p* value
Age	0.040	0.74
Gender (0; female, 1; male)	−0.046	0.71
BMI	−0.081	0.51
Prior treatment for osteoporosis (0; No, 1; Yes)	−0.262	0.03*
Active vitamin D analog supplementation period before ZA infusion	−0.195	0.11
LS BMD T-score	0.088	0.45
FN BMD T-score	−0.068	0.10
Serum cCa at baseline	0.023	0.85
log CCr at baseline	−0.106	0.39
log TRACP-5b	0.358	0.003**
log iPTH	−0.032	0.80
log 25 (OH)D	−0.104	0.40

$p < 0.05$ was considered a statistically significant difference (*$p < 0.05$, **$p < 0.01$).
BMD Bone mineral density, *BMI* Body mass index, cCa Corrected calcium, *CCr* Creatine clearance, *FN* femoral neck, i*PTH* intact parathyroid hormone, *LS* lumbar spine, *TRACP-5b* tartrate-resistant acid phosphatase 5b, *ZA* zoledronic acid, *25(OH)D* 25-hydroxycholecalciferol.

serum 25(OH)D level and APRs is controversial [20,27,28]. In this study, the discrepancy in 25(OH)D may be explained by the extremely lower level of 25(OH)D at baseline [means 10.5 ng/mL] and daily supplementation of active vitamin D analog in all patients.

Another concern during the early recovery period is hypocalcemia associated with vitamin D deficiency and perioperative overhydration when ZA is administered in the first 2 weeks of the perioperative period [4]. Previous studies argued that many patients who undergo surgery have hypocalcemia in the perioperative period, and hypocalcemia is associated with perioperative complications such as delirium [29-31]. In this study, the mean serum 25(OH)D before HF surgery was 10.5 ng/mL, and half of all patients had severe vitamin D deficiencies. However, serum cCa level significantly increased despite the early perioperative period. We speculate that the main reason why serum cCa level increased during this period may be explained by daily supplementation of active vitamin D analog after admission for a mean of 12.8 days. Hypocalcemia associated with vitamin D deficiency and perioperative overhydration during the perioperative period after HF surgery may be prevented by active vitamin D analog supplementation, and no patients had hypocalcemia before ZA administration.

In the HORIZON-PFT study, 49 patients (1.3%) had transient and asymptomatic hypocalcemia (<8.3 mg/dL) 9 to 11 days after the first ZA infusion [17], but few studies have investigated the transition of serum cCa levels after the first ZA infusion in patients with osteoporosis [21]. Takada et al. reported that 104/184 (56.5%) patients received active vitamin D analog before the first ZA infusion, and none of the patients showed hypocalcemia (<8.3 mg/dL) at 1 month after the first ZA infusion. However, the serum Ca levels in patients who had not taken other BPs for more than 2 years before ZA administration or received BPs were significantly lower compared to those who had continuously received other BPs until ZA administration, even when combined with active vitamin D analog [21]. Serum Ca decrease induced by ZA was significantly higher in patients who were not co-administered with active vitamin D analog, and they suggested that the combine used of active vitamin D analog is preferable in patients without a history of BP administration [21]. In our study, all HF patients also received active vitamin D analog, no patients exhibited symptomatic hypocalcemia, and transient hypocalcemia (<8.3 mg/dL) was observed in 1 patient on day 1 and 5 patients on day 7, although the majority of patients had no pretreatment with antiresorptive agents or coexisting vitamin D deficiencies.

In this study, multiple regression analysis revealed that serum TRACP-5b at baseline and cCa level on day 0 was associated with ΔCa_{0-7d}. The relationship between serum TRACP-5b at baseline and ΔCa_{0-7d} suggests that patients who depend on high bone turnover to maintain normal serum Ca level are more susceptible to bone turnover suppression by ZA. Measuring serum cCa levels on day 7 after ZA administration is important clinically, and measuring serum cCa levels after day 7 is necessary, especially in patients with high serum TRACP-5b level at baseline.

Our study has several limitations. First, the number of patients was relatively small in one-treatment arm. However, withholding anti-osteoporosis drugs could cause subsequent fractures; therefore, it would be ethically unacceptable to set up a control group that did not receive ZA therapy after HF. Second, this study included some male patients with HF. Because most previous studies included only postmenopausal female and reported the adverse events related to first ZA administration, a simple comparison was difficult because of differences in the male/female ratio. Third, the effects of ZA administration after HF repair surgery for BMD in the lumbar spine and contralateral hip and further fracture prevention were not elucidated. Further studies with larger samples are needed to assess the effectiveness of ZA administration during the perioperative period after HF. Fourth, the effects for hip fracture healing were not fully elucidated due to the small number of patients and a lower follow-up rate after HF, although previous studies concluded that ZA infusion after HF surgery has no adverse effects on

fracture healing and the timing of ZA infusion also has no effect on fracture healing [9,32,33].

However, an important strength of the study was that body temperature was recorded by medical staff in detail and the incidence of APRs was precisely investigated in all patients. Additionally, the transition of serum cCa levels after the first ZA infusion was investigated in detail.

5. Conclusion

The initiation of oral BPs has been strongly recommended as the first-line antiosteoporosis therapy for patients who receive HF surgery, but it seems very difficult for most HF patients to continue visiting the hospital and adhere to the oral BP regimen. This study reveals that tolerability of the first ZA infusion within one to two weeks after HF surgery is generally good in combination with antipyretic analgesics and active vitamin D analog. Once-yearly ZA infusion during the perioperative period seems a useful option to prevent secondary fracture in HF patients who have difficulty starting or continuing oral antiosteoporosis drugs.

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Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was conducted in accordance with the approval of the ethical review boards of our institution (2019-03-02). Informed consent was obtained from all individual participants included in the study.

CRediT authorship contribution statement

Masafumi Kashii: Conceptualization, data curation, formal analysis, Interruption of results, writing – original draft.

Takashi Kamatani: Investigation, data curation, writing – review & editing.

Shingo Abe: Investigation, data curation, writing – review & editing.

Ayanori Yoshida: Investigation, data curation, writing – review & editing.

Kota Koizumi: Investigation, data curation, writing – review & editing.

Naoko Mizuno: Investigation, data curation, writing – review & editing.

Kengo Yamamoto: Conceptualization, writing – review & editing, supervision.

Kohji Kuriyama: Conceptualization, writing – review & editing, supervision.

Hideki Yoshikawa: Conceptualization, writing – review & editing, supervision.

Declaration of competing interest

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