Surgical trauma and low-dose methylprednisolone modulate the severity of the acute-phase response induced by zoledronic acid infusion

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Abstract. The aim of the present study was to investigate risk factors for the development of an acute-phase response (APR) associated with the initial zoledronic acid (ZA) infusion in patients undergoing surgery, and to assess whether its onset may be reduced by post-dose administration of low-dose methylprednisolone (MP) or acetaminophen. A retrospective study of patients with osteoporosis who attended the departments of orthopedics and endocrinology of a single hospital and received 5 mg ZA was conducted; the patients included surgical and non-surgical cases. A total of 450 ZA-naïve patients who were treated with acetaminophen following ZA infusion were stratified based on whether they suffered APR (APR^+) or not (APR^-). In addition, 155 of the aforementioned acetaminophen-treated patients (acetaminophen group) were compared with another 32 patients from the orthopedic department who were treated with MP immediately following ZA infusion (MP group). Inflammatory marker levels were significantly higher in APR^+ patients than in APR^- patients, and the odds ratios of experiencing APR following minimally invasive or open surgery were found to be 3.54 ($P<0.001$) and 5.71 ($P<0.001$), respectively, compared with non-surgical intervention after multiple adjustments. C-reactive protein levels prior to dosing were positively correlated with body temperature ($r=0.023$; $P<0.001$). The severity of APR also exhibited a negative correlation with 23-hydroxyvitamin D3 levels ($r=-0.006$; $P<0.05$). Patients treated with MP following surgery and ZA infusion had a significantly lower incidence of APR compared with those treated with acetaminophen (6.3 vs. 62.6%; $P<0.05$). However, no significant differences were observed in bone mineral density between the MP and acetaminophen groups at 12 months post-surgery. The results of the present study suggest that surgical trauma serves a key role in ZA-associated APR, and low-dose MP may a suitable post-dose treatment to manage the symptoms of APR in patients undergoing surgery.

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Introduction

Bisphosphonates (BPs) are the most commonly prescribed medication for the management of osteoporosis (1). Zoledronic acid (ZA) is a new generation BP that can be administered intravenously once yearly. It comprises a double nitrogen-containing structure (an imidazole ring) that results in a high affinity for hydroxyapatite and induces a 10-fold increased inhibition of bone resorption compared with daily oral BPs (2,3). However, acute-phase response (APR) is more common with ZA compared with other BPs (4). APR is characterized by the following: Transient mild fever, malaise, flu-like symptoms, digestive symptoms, headache and dizziness, all occurring within 3 days of the initial drug infusion (5-8). The molecular mechanisms of APR have recently been elucidated. It has been suggested that ZA leads to the accumulation of isopentenyl pyrophosphate and dimethylallyl pyrophosphate, which are potent agonists of the γδT cell receptor, as upstream metabolites of farnesyl phyrophosphate synthase in the mevalonate pathway (9-16). These agonists are naturally recognized by γδT cells, inducing the activation and release of tumor necrosis factor (TNF)-α, TNF-β, interferon (IFN)-γ, interleukin (IL)-2 and IL-6, which are pro-inflammatory cytokines involved in the development of APR (9-16).

It has been observed by the present authors that patients treated with ZA in the early post-operative period develop APR more readily. To the best our knowledge, no previous studies have reported the risk factors for APR associated with the early administration of ZA post-surgery. However, some studies have suggested that advanced age, supplementation of

vitamin D, prior use of oral BPs and nonsteroidal anti-inflammatory drugs (NSAIDs) are relieving factors for APR (5-8,16).

Previous studies have reported that NSAIDs, such as acetaminophen, effectively alleviate the symptoms of APR (5-8), however, the protective efficacy of NSAIDS was found to be unsatisfactory in patients who underwent ZA therapy soon after surgery. At present, there is no evidence suggesting that low-dose glucocorticoids (GC), such as methylprednisolone (MP), have strong anti-inflammatory properties for the prevention of APR. Therefore, further investigation is required to obtain data to ascertain whether MP may be an effective alternative to acetaminophen.

The aim of the present study was to evaluate the effects of surgical trauma on the development of APR and to investigate the efficacy of low-dose MP in preventing APR associated with the early post-surgical administration of ZA using clinical data from the orthopedics and endocrinology departments at a single hospital.

Materials and methods

Patients. A total of 482 patients aged from 49 to 89 years were recruited in this hospital-based, retrospective study including 77 males and 405 females at the First Affiliated Hospital of Nanjing Medical University (Nanjing, China) from January 2012 to December 2014. Patients receiving their initial ZA infusion for osteoporosis (17), some of whom received ZA at 1 week after orthopedic surgery, were included in the present study. Patients with absorption fever or infection post-surgery were excluded, as this had the potential to affect the observation of APR symptoms. Exclusion criteria included a history of cancer, hyperparathyroidism, and previous use of parathyroid hormone (PTH), strontium, sodium fluoride, intravenous or oral BPs, recent or chronic corticosteroid therapy, statins or immune therapy. Furthermore, patients with severe injuries, liver or kidney disease, or recent or scheduled dental surgery were ineligible. The present study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University and written informed consent was obtained from all patients.

Study design and procedures. All subjects were treated with cholecalciferol (Roche Diagnostics, Basel, Switzerland) 800 IU/day and Caltrate (Pfizer, Inc., New York, NY, USA) 1,200 mg/day orally from the time of hospitalization as vitamin D and calcium supplements, respectively. This treatment was continued following ZA infusion. All patients received 5 mg ZA (Novartis International AG, Basel, Switzerland) via intravenous infusion over 15 min. Prior to the administration of ZA, patients were supplemented with 1 g calcium gluconate (Qingdau Huanghai Pharmaceutical Co., Ltd., Qingdao, China) in 0.9% saline to avoid acute hypocalcemia.

In the first part of the study, 450 acetaminophen-treated patients were divided into the following groups: Open surgery (OS; n=93), minimally invasive surgery (MIS; n=135) and non-surgery (NS; n=222) according to the degree of surgical trauma. Percutaneous vertebroplasty, percutaneous kyphoplasty and percutaneous cannulated screw fixation were considered as MIS approaches. OS approaches comprised other orthopedic surgery methods associated with spinal and articular implants. Patients in the endocrinology department who had not experienced fresh fractures due to fragility within the previous 6 months, including vertebral compression fractures and hip fractures, were defined as NS subjects. All 450 patients received 0.3 g acetaminophen (Bayer AG, Leverkusen, Germany) orally twice daily on the day of the infusion and as required for the next 3 days (5,8) (Fig. 1).

In the second part of the study, 187 patients who had undergone orthopedic surgery, which included 155 of the 450 patients from the first part of the study and 32 unrelated cases from the orthopedics department, were further evaluated to compare the efficacy and safety of acetaminophen and low-dose MP. Patients without GC contraindications, such as active ulcer or glaucoma, and who completed the 1-year follow-up were included. The 155 patients that met the above criteria from the OS and MIS subgroups (66 and 89 patients, respectively) constituted the acetaminophen group. The 32 unrelated cases had been immediately treated with 40 mg MP (Pfizer, Inc.) in 0.9% saline daily for 2 days after ZA infusion subsequent to surgery, and constituted the MP group. The MP group included 16 patients who had undergone OS and 16 who had undergone MIS. Fever occurring subsequently was treated with acetaminophen as required in the acetaminophen and MP groups (Fig, 1).

Biochemical measurements and bone mass density (BMD) assessment. Samples of fasting peripheral blood at rest were taken as a baseline on the morning prior to ZA infusion. The biochemical parameters analyzed in this study were calcitonin (CT), type I collagen cross-linked C-telopeptide (CTx), N-telopeptide (NTx), bone gla protein (BGP), PTH, 25-hydroxy-vitamin D3 [25(OH)D], serum Ca^{2+}, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). CT levels were assessed using a radioimmunoassay kit (CT-10161; Amresco LLC, Solon, OH, USA) according to the manufacturer's protocol. CTx and NTx were assessed using electrochemiluminescence immunoassay kits (PP-US-07407 and PP-US-05294, respectively; Roche Diagnostics) according to the manufacturer's protocol. BGP levels were assessed using a chemiluminescent microparticle immunoassay (MAGLUMI 2000 Plus; Shenzhen New Industries Biomedical Engineering Co., Ltd., Shenzhen, China). PTH levels were evaluated via chemiluminescence immunoassay (Immulite 2000; Siemens AG, Munich, Germany). 25(OH) D levels were assessed using an ELISA kit (LIAISON; cat. no. 310980; DiaSorin, Saluggia, Italy). Ca^{2+} levels were analyzed using the calcium ion complexation EDTA titration method as previously described (18). CRP levels were assessed using immunoturbidimetry on a Sat450 analyzer (AMS s.r.l, Marcianise, Italy). ESR was recorded using an automatic analyzer (Monitor 100; ELITechGroup, Inc., Smithfield, RI, USA). In addition, the levels of TNF-α, IL-2 and IL-6 at baseline prior to administration of ZA were measured in a subgroup of 40 patients (16 OS patients, 14 MIS patients and 10 NS patients) using ELISA kits (CSB-E04740 h, CSB-E04626 h and CSB-E04638 h, respectively; Cusabio Biotech Co., Ltd., Wuhan, China).

Dual-energy X-ray absorptiometry (Hologic, Bedford, MA, USA) of the spine or hip was used to measure BMD

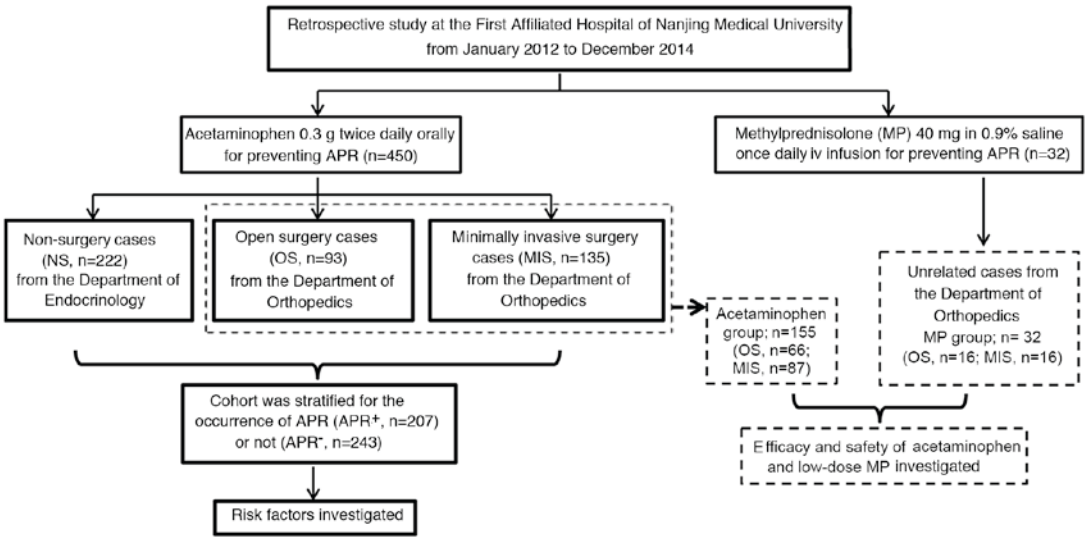

Figure 1. Study design flowchart. APR, acute-phase response.

prior to and 1 year following the administration of ZA and the neck and spine of T-score were recorded.

Clinical observation. Post-surgery, all symptoms including APR and serious adverse events, such as delayed healing, incision infection, cardiovascular events and stroke, were assessed via the continuous monitoring of vital signs and physical assessments. Adverse events were categorized according to codes from the Medical Dictionary for Regulatory Activities (19) as previously described (6). APR symptoms and the axillary body temperature were recorded eight times per day. APR onset was categorized as the presence of fever (temperature >37.3˚C) or the presence of at least one other APR symptom, such as myalgia, headache, dizziness, nausea, vomiting or eye pain. The highest post-dose body temperatures recorded in the 3 days following infusion were used as an indicator of the severity of APR.

Patients were monitored via telephone interviews for 1 year post-treatment. The incidence of bisphosphonate-related osteonecrosis of jaw (BRONJ) and new/re-fracture within this time was recorded. X-ray examinations were necessary for the diagnosis of BRONJ, and magnetic resonance imaging was performed to confirm new/re-fracture.

Statistical analysis. Analysis was performed using SPSS 19.0 (IBM SPSS, Armonk, NY, USA). All data are expressed as the mean ± standard deviation for each group. Categorical variables and proportions were analyzed using the Chi-square test. The demographic characteristics, bone turnover bio-parameters and inflammatory cytokines were compared according to the APR group (APR^+, APR^-) using analysis of variance and the Wilcoxon rank test for continuous variables. Logistic regression analysis was performed to determine the potential risk factors of experiencing at least one APR. The odds ratio (OR) included 95% confidence intervals (95% CIs). Associations between continuous variables were examined using simple and multivariate linear regression.

A paired t-test was used to compare BMD prior to and following treatment. Increases in BMD were compared using independent t-tests. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Risk factors for APR. The demographic, clinical and biochemical characteristics of the 450 patients immediately treated with acetaminophen are presented in Table I. APR^+ patients had significantly lower levels of 25(OH)D ($P<0.001$; Table I) and significantly higher levels of CRP, TNF-α, IL-2 and IL-6 compared with APR^- patients ($P<0.001$; Table I). The ESR was significantly higher in APR^+ patients compared with APR^- patients ($P<0.001$; Table I). No significant differences in gender, age, body mass index (BMI), CT, CTx, NTx, BGP, PTH or BMD was observed between the APR^+ and APR^- groups.

In the APR^+ group, 25(OH)D levels were 36.12±17.26 nmol/l, which is considerably below the normal reference range and considered to indicate a vitamin D deficiency (20). Based on this result, the baseline characteristics influencing a patient's likelihood of suffering APR were investigated by performing single-factor and multi-factor logistic regression. Variables considered included age (≥65 or <65 years), gender, BMI (≥24 or < 24 kg/m^2), 25(OH)D levels (≥50 or <50 nmol/l), surgical approaches (MIS and OS) and disease history (diabetes mellitus, hypertension and chronic obstructive pulmonary disease). The OR for APR in 25(OH)D-deficient (<50 nmol/l) compared with 25(OH)D insufficient or sufficient (≥50 nmol/l) patients was 2.57 ($P<0.001$) unadjusted, or 2.12 ($P=0.007$) after multiple adjustments; the OR in the MIS group compared with the NS group was 3.87 ($P<0.001$) unadjusted, or 3.54 ($P<0.001$) after multiple adjustments; and in the OS group compared with the NS group was 6.40 ($P<0.001$) unadjusted, and 5.71 ($P<0.001$) after multiple adjustments. The results of this analysis revealed that 25(OH)D-deficient and surgical patients had an elevated risk of APR, particularly following major trauma (Fig. 2).

Table II lists simple and multiple linear regression coefficients between continuous variables including age, BMI, levels of Ca^{2+}, CT, CTx, NTx, BGP, PTH and 25(OH)D and pre-dose

Table I. Demographic, clinical and biochemical characteristics of the study population according to APR development (APR^+/APR^-).

Characteristic	Total cases	APR^+	APR^-	P-value
Patients (n)	450	207	243	
Sex (M/F)	72/378	38/169	34/209	0.25
Age (years)	66.8±9.3	66.7±8.5	66.8±9.9	0.94
BMI (kg/m^2)	23.4±2.8	23.5±2.9	23.4±2.7	0.75
Ca^{2+} (mmol/l)	2.26±0.13	2.27±0.12	2.26±0.13	0.59
CT (pg/ml)	43.11±27.21	43.62±28.52	42.67±26.03	0.72
CTx (ng/ml)	0.50±0.36	0.52±0.38	0.49±0.34	0.38
NTx (ng/ml)	39.78±32.50	41.34±34.27	38.46±30.85	0.32
BGP (ug/l)	19.46±11.18	20.12±11.48	18.89±10.89	0.26
PTH (pg/l)	32.09±13.07	32.64±14.13	31.63±12.07	0.48
25(OH)D (nmol/l)	41.85±20.37	36.12±17.26	46.74±21.51	<0.001
T-score neck (SD)	-3.17±0.82	-3.25±0.75	-3.11±0.87	0.071
T-score spine (SD)	-2.81±0.73	-2.77±0.73	-2.84±0.73	0.311
CRP (mg/l)	9.29±12.47	14.07±15.32	5.22±7.22	<0.001
ESR (mm/h)	19.29±13.36	23.85±15.52	15.41±9.63	<0.001
TNF-α (ng/ml)[a]	0.622±0.237	0.747±0.214	0.452±0.144	<0.001
IL-2 (ng/ml)[b]	11.44±5.06	13.92±4.52	8.08±3.68	<0.001
IL-6 (pg/ml)[c]	194.1±64.1	222.3±63.4	154.7±40.1	<0.001

Data are presented as the mean ± SD. [a]N=40, [b]n=23 and [c]n=17. APR, acute-phase response; M, male; F, female; BMI, body mass index; CT, calcitonin; CTx, type I collagen cross-linked C-telopeptide; NTx, N-telopeptide; BGP, bone gla protein; PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D3; SD, standard deviation; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; TNF, tumor necrosis factor; IL, interleukin.

Table II. Simple and multiple linear regression coefficients between continuous variables and fever.

Variable	Regression coefficient
Age	-0.08
BMI	0.036
Ca^{2+}	0.137
CT	0.102
CTx	0.041
NTx	0.009
BGP	0.063
PTH	-0.107
25(OH)D	-0.006[a]
CRP	0.023[b]

[a]P<0.05; [b]P<0.001. BMI, body mass index; CT, calcitonin; CTx, type I collagen cross-linked C-telopeptide; NTx, type I collagen cross-linked N-telopeptide; BGP, bone gla protein; PTH, parathyroid hormone; CRP, C-reactive protein.

CRP levels, with elevated body temperature. 25(OH)D levels were significantly negatively correlated (P<0.05) with the presence of fever (a marker of APR), whereas pre-dose CRP levels were positively correlated with fever (P<0.001).

These results suggest that surgical trauma is associated with APR incidence, and the association between CRP, which served to quantify the increased levels of inflammation in the early phase following surgery, and fever has a dose-response relationship. These results also indicate that clinically significant differences in the severity of APR may be associated with vitamin D deficiency.

Efficacy assessments. To minimize the potential side effects of GC, 40 mg MP was administered, which is the minimum injectable dose to prevent APR (21). No significant difference was observed in baseline demographic and clinical characteristics between groups. The incidence of APR was significantly lower in the MP group compared with the acetaminophen group (P<0.001; Table III). Similar results were observed for fever morbidity (P<0.05; Table III).

Safety assessments. ZA administration did not appear to induce adverse effects in any participants. At the 12-month follow-up, few cases of new/re-fracture were reported, and the frequency was similar in each group (1 case in the MP group and 2 cases in the acetaminophen group). There were no reports of spontaneous BRONJ.

No significant differences were observed in baseline BMD between groups. At the 12-month follow-up, no significant difference in BMD increase was observed for the lumbar vertebra or hip, including the femoral neck, trochanteric or intertrochanteric region (Fig. 3). However, BMD in Ward's region showed a significantly greater increase in the MP group compared with the acetaminophen group (P<0.05; Fig. 3).

Table III. Demographic characteristics and APR symptoms in the MP and acetaminophen groups.

Characteristic	Total cases (n=187)	MP group (n=32)	Acetaminophen group (n=155)	P-value
Age	68.9±8.6	70.6±9.1	68.6±8.5	0.230
Gender (M/F)	27/160	5/27	22/133	0.509
BMI (kg/m^2)	23.6±3.0	22.7±3.5	23.8±2.9	0.082
25(OH)D (nmol/l)	42.01±21.18	39.48±18.43	42.64±21.72	0.397
CRP (mg/l)	20.87±13.11	23.07±19.32	20.42±11.45	0.459
OS/MIS	82/105	16/16	66/89	0.558
APR (all symptoms)	99 (52.9%)	2 (6.3%)	97 (62.6%)	<0.001
Fever	97 (51.9%)	2 (6.3%)	95 (61.3%)	<0.001
Other symptoms	28 (15.0%)	1 (3.1%)	27 (17.4%)	0.053

Data are presented as the mean ± standard deviation, or as the number (percentage) in the cohort. Other symptoms include malaise, flu-like syndrome, digestive symptoms, headache and dizziness. APR, acute-phase response; MP, methylprednisolone; M, male; F, female; BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D3; CRP, C-reactive protein; OS, open surgery; MIS, minimally invasive surgery.

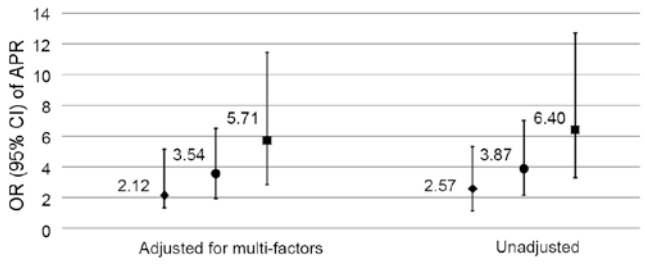

Figure 2. Risk of APR development. The multi-factors adjusted for are age, gender, body mass index, 25(OH)D levels, surgical approach and disease history (diabetes, hypertension and chronic obstructive pulmonary disease). The diamonds represent the OR of APR in 25(OH)D-deficiency (<50 nmol/l) compared with 25(OH)D insufficiency or sufficiency (≥50 nmol/l). The circles represent the OR of APR in open surgery compared with NS. The squares represent the OR of APR in minimally invasive surgery compared with NS. The bars represent the 95% CI. APR, acute-phase response; 25(OH)D, 25-hydroxyvitamin D3; OR, odds ratio; CI, confidence interval; NS, non-surgery.

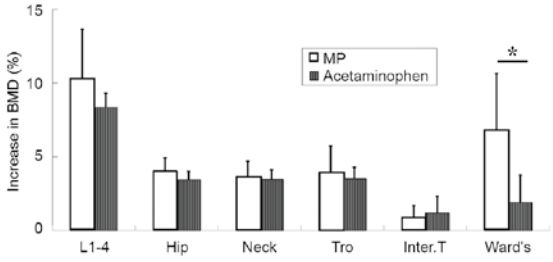

Figure 3. BMD improvement in different areas at the 12-month follow-up. Data are presented as the mean and standard deviation. *P=0.033 as indicated. BMD, bone mass density; MP, methylprednisolone; Tro, trochanteric; Inter.T, intertrochanteric; Ward's, Ward's region.

Discussion

The results of the present study demonstrate that the surgical method used and subsequent baseline levels of inflammation are crucial determinants of the development of an APR in patients with osteoporosis. As a major acute-phase protein, CRP is secreted by liver cells following trauma; therefore, CRP levels may be used to assess inflammatory levels and quantify the degree of surgical trauma with high sensitivity (22-24). Additionally, cell cytokines such as IL-2, IL-6 and TNF-α are upregulated by surgical trauma, and their activation subsequently upregulates the expression of other inflammatory factors in activated adjacent γδT cells (22,23). In the present study, high levels of CRP post-surgery and prior to treatment were correlated with an elevation in body temperature, i.e., the severity of APR in patients treated with ZA. Plasma inflammatory cytokine concentrations following a moderate trauma stimulus typically recover to basal levels within 1 week (23); however, in the present study the incidence of APR was notably higher when ZA was administered within 1 week of surgery than has been reported in other literature (6,7).

It has been reported that vitamin D is able to modulate immunological function and reduce levels of IFN-γ, TNF-β and IL-2 in T cells (25,26), and it is believed that that 25(OH)D deficiency may lead to the development of APR (27). This provides an explanation for the finding in the present study that 25(OH)D is an important risk factor for APR. It has been suggested that the attainment of adequate levels of 25(OH)D (>100 nmol/l) prior to the first infusion may reduce the incidence of fever (27).

The present study demonstrated that acetaminophen was unable to control or prevent APR within 1 week post-surgery due to its limited anti-inflammatory function; however, low-dose MP administration effectively ameliorated the ZA-induced increase in body temperature. To the best of our knowledge, no clinical observation data for low-dose MP and APR in ZA-naïve patients in the early postoperative period are available. In a GC-induced osteoporosis subpopulation treated with ZA, the frequency of APR was reported to be slightly lower than that in primary osteoporosis (6,28,29), which may be attributable to the use of GC during therapy. No significant differences were reported in the incidence of serious adverse events, such as arrhythmia or serious atrial fibrillation, BRONJ or re/new fractures between the two groups (6,28,29). The most common adverse event reported in the present study was fever, together with associated symptoms such as chills and flushes, which occurred in 61.3% of acetaminophen-treated

subjects after ZA infusion, compared with <6.3% of the MP group. In addition, the patients in the acetaminophen group reported a number of other symptoms, such as myalgia, headache, malaise, and fatigue, which are probably a reflection of widespread inflammatory changes.

Compared with orally administered BPs, ZA is advantageous due to decreased incidence of gastrointestinal tract reactions, a higher absorption rate, and a regimen of once-yearly infusions which guarantees medication compliance and adherence (30-33). A previous study reported that ~78.7% patients prefer a once-yearly infusion regimen (34). A number of studies have demonstrated that ZA is associated with a significant improvement in clinical outcomes following orthopedic surgery in patients with osteoporosis (35-41). However, it is unclear whether BPs are helpful or harmful in acute fracture healing or spinal fusion. Two meta-analyses of randomized controlled trials reported that even early administration of BPs post-surgery did not delay fracture healing or spinal fusion time, either radiologically or clinically (42,43). Animal studies have demonstrated that ZA treatment immediately post-surgery may have a positive effect on spinal fusion in patients with osteoporosis, with no adverse effects on the healing process of bone grafts (44). Considering the beneficial aspects of BP treatment for patients with osteoporosis, ZA infusion following fracture fixation surgery, spine fusion surgery or arthroplasty appears to be a viable treatment option.

In the present study, ZA administration was not tolerated in some acetaminophen-treated patients, inducing a higher incidence of influenza-like illness and pyrexia events postoperatively. The ability to reduce the incidence and severity of APR symptoms with low-dose MP ensures that any post-treatment effects are kept to an acceptable level post-surgery.

The present study had several limitations. Firstly, its retrospective nature may have resulted in selection bias of the patients. Secondly, the small sample size may have have insufficient statistical power to detect slight effects. Finally, changes in bone metabolism markers, renal function and hypocalcemia were not assessed.

In conclusion, surgical trauma is an important determining factor for the occurrence of APR. For patients undergoing surgery, low-dose MP appears to have potential as a therapeutic application for preventing APR induced by ZA infusion. These findings may provide a feasible and safe treatment for the management of APR symptoms.

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