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Clinical Study

Clinical effect of early bisphosphonate treatment for pyogenic vertebral osteomyelitis with osteoporosis: An analysis by the Cox proportional hazard model

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Abstract

BACKGROUND CONTEXT: Patients with pyogenic vertebral osteomyelitis (PVO) are expected to have an increased risk of bone loss. Therefore, early bisphosphonate therapy would be clinically effective for PVO patients with osteoporosis.

PURPOSE: This study aimed to investigate the effect of bisphosphonate on clinical outcomes of PVO patients with osteoporosis.

STUDY DESIGN/SETTING: A retrospective comparative study.

PATIENT SAMPLE: PVO patients with osteoporosis.

OUTCOME MEASURES: Four events of interest for Cox proportional hazard model included surgical treatment, recurrence of infection, subsequent fracture of adjacent vertebral bodies, and death.

METHODS: PVO patients were divided into three groups: group A (initiation of bisphosphonate within 6 weeks after PVO diagnosis), group B (initiation of bisphosphonate between 6 weeks and 3 months after PVO diagnosis), and group C (no treatment for osteoporosis). Cox proportional hazard model was used for the four events of interest.

RESULTS: A total of 360 PVO patients with osteoporosis were investigated for the four events of interest. Group A had significantly lower hazard ratios for undergoing later (>6 weeks after diagnosis) surgery than group C ($p = .014$) despite similar occurrences of overall surgery. A significant difference was also observed in the occurrence of subsequent fractures at adjacent vertebral bodies ($p = .001$ for model 1 and $p = .002$ for model 2). Groups A and B had significantly lower hazard ratios for subsequent fracture than group C. No significant differences were observed in the hazard ratios of recurrence and death among the three groups.

CONCLUSIONS: Early bisphosphonate treatment in PVO patients with osteoporosis was associated with a significantly lower occurrence of subsequent vertebral fracture at adjacent vertebral bodies and lower occurrence of subsequent surgery.

Keywords: Bisphosphonate; Pyogenic vertebral osteomyelitis; Recurrence; Subsequent fracture; Surgery; Survival

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Introduction

Bisphosphonates, pyrophosphate analogs that strongly bind to hydroxyapatite, are primary drugs for patients with osteoporosis. Numerous studies demonstrated their effectiveness on several disease conditions related to imbalance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption [1,2]. A number of high-quality clinical trials have consistently shown that bisphosphonate significantly increases bone mineral density (BMD) and reduces the incidence of fragility fractures [1]. However, recent publications have addressed concerns related to the long-term use of bisphosphonate. The association between prolonged suppression of bone turnover by bisphosphonate and atypical femoral fracture or delayed healing is evident from the result of numerous studies [3,4]. Concerns are also increasing regarding the association between the long-term use of bisphosphonate and bisphosphonate-related osteonecrosis of the jaw [5].

Fortunately, the negative effect of bisphosphonates on fracture healing does not seem to produce meaningful clinical differences [6]. According to the recent articles, bisphosphonate did not significantly affect the clinical outcome of osteoporotic vertebral fracture [7] and rather reduced time to fusion in osteoporotic patients with spinal fusion [8]. In addition, early bisphosphonates significantly reduced the rate of new fracture and improved patients' survival after repair of hip fracture [9,10].

Despite recent advancement in treatment of bone and joint infection including magnetic resonance imaging (MRI) [11,12] and development of new antibiotics [13], high success rates of antibiotic therapy have not yet been achieved in osteomyelitis due to the anatomical characteristics of bones [14]. Advanced or complicated osteomyelitis of long bones often requires surgical treatment including radical debridement, temporary stabilization, and subsequent bone graft. Surgical treatment is more complicated in vertebral osteomyelitis. During treatment for pyogenic vertebral osteomyelitis (PVO), significant bone loss can occur directly by causative organisms and indirectly by disuse-type bone loss (from bed rest and brace immobilization) and limited sunlight exposure (from long hospitalization for intravenous antibiotics) [15–17]. Such bone loss could be fatal on bone health of elderly PVO patients [18] with several medical comorbidities [19]. It can induce structural instability, which leads to neurologic deficit, spinal deformity, and even death [19,20]. Therefore, permanent and extensive stabilization using spinal instrument is often required after debridement or neural decompression. Such long instrumentation sometimes fails in patients with severe bone loss [21]. In addition, spinal instrumentation during ongoing infection may not only disturb control of spinal infection but also severely limits mobility of patients after infection control [22]. Therefore, minimizing vertebral bone loss should be one of the most important goals during the long treatment period of PVO.

However, medical treatment for bone loss during PVO treatment has not been an interest to spine surgeons or infectious disease specialists [23]. No studies investigating the effect or safety of bisphosphonate in PVO patients, although bisphosphonate can be extremely helpful for preventing bone loss and improving clinical outcome in PVO patients, have been conducted. We hypothesized that early bisphosphonate therapy would be clinically effective for PVO patients with osteoporosis by limiting structural destruction, reducing the need for surgery, preventing subsequent vertebral fracture after PVO, and eventually increasing survival after PVO. This retrospective cohort study aimed to investigate the effect of bisphosphonate on clinical outcome of PVO patients with osteoporosis.

Materials and methods

Study design and ethics

A retrospective case review was performed on PVO patients with osteoporosis who visited our institution between January 2000 and April 2017. This study was designed and conducted using the format recommended by the Strengthening the Reporting of Observational studies in Epidemiology guidelines [24]. The study protocol of the current study was approved by the Institutional Review Boards of our institution.

Study patients

Our university medical center is one of the largest medical institutions in our country, consisting of six general hospitals. This study was performed in the main institute among the six general hospitals. As a main institute of our medical center, our hospital serves as a tertiary referral center from not only the other five general hospitals but also from numerous local hospitals. Elderly patients (aged $\geq$60 years) with microbiologically confirmed PVO were included. PVO was defined using the following criteria: (1) suggestive clinical symptoms, (2) accompanying typical radiological features on MRI, and (3) microbiological identification [25]. Typical radiologic findings include [26–28] (1) alteration of the normal marrow signal intensity with ill-defined margin including decrease on T1-weighted sequences and increase on fat-suppressed T2-weighted sequences, (2) involvement of disk space and two adjacent vertebral bodies, (3) periosteal reaction and adjacent soft tissue edema, and (4) soft tissue abscess especially in epidural space from gadolinium contrast imaging. Microbiological confirmation included isolation from blood culture, computed tomography guided needle biopsy, or surgical biopsy. Only PVO patients with osteoporosis at the time of PVO diagnosis were included, because long-term radiologic and clinical follow-up including BMD was only available for the PVO patients with osteoporosis.

Patients were excluded from their medical records if they had known diseases or medications related to

abnormal bone metabolism including parathyroid disorders, the Paget disease, skeletal metastasis, anticonvulsant drugs, corticosteroid, and previous medication for osteoporosis (Fig. 1). Patients with recent fracture (within 6 months before PVO diagnosis) were also excluded. Patients with severe neurologic deficit (American Spinal Injury Association impairment scale A, B, and C) [29] at the time of PVO diagnosis were excluded regardless of the cause of neurologic deficit, because these groups of patients are less sensitive to bisphosphonate treatment [30], and their clinical outcomes are greatly influenced by their neurologic status. Patients who received the initial osteoporosis treatment except for bisphosphonate were also excluded. Other reasons for exclusion were incomplete medical records or imaging data.

Data collection

Medical records were retrospectively reviewed for demographic information, underlying illness, smoking status, isolated microorganism, duration of antibiotics, medical or surgical treatment for PVO, clinical outcomes for PVO, and treatment for osteoporosis. Smoking history was retrieved as nonsmoker, exit smoker, and current smoker. Charlson Comorbidity Index, a validated instrument as a predictor of morbidity due to comorbid conditions, was derived from medical records [31]. Initial laboratory results including C-reactive protein (CRP) and serum levels of calcium, phosphonate, nonspecific alkaline phosphatase, and creatinine were also collected.

From the initial spine MRI at diagnosis of PVO, the primary region of PVO (cervical, thoracic, or lumbar regions) and the number of involved levels (counted by the number of involved vertebral bodies) were identified. If PVO included two regions, the more severe region (decided by the degree of vertebral body destruction) was recorded as the primary region. From the initial x-ray, the degree of kyphosis was assessed by the Cobb angle between (MRI-defined) most upper and lower involved vertebral bodies from lateral radiograph [32].

Definitions

According to the previous reports [33], recurrence was defined as patients who had recurrent symptoms and signs after the completion of antibiotic treatment and received a second course of parenteral antibiotics. Subsequent vertebral fracture was defined as fractures of the vertebrae (except for the infected vertebrae evidenced by initial or follow-up imaging study) that occurred after diagnosis of PVO. The semiquantitative technique by Genant et al. [34] was used to evaluate the subsequent fracture at adjacent vertebral bodies in the follow-up x-ray, and a reduction in vertebral height (anterior, posterior, or middle) of 20% or more was diagnosed as a subsequent fracture.

Severity of infection in PVO patients was evaluated by the validated classification by Pola et al. [35], who divided pyogenic spondylodiscitis into following three types: (1) type A, cases without biomechanical instability neither acute neurological impairment or epidural abscesses; (2) type B, cases with radiological evidence of significant bone destruction or biomechanical instability without acute neurological impairment or epidural abscesses; and (3) type C, cases with epidural abscesses or acute neurologic impairment.

In our institute, both spine surgeons and infectious disease specialists were involved in the multidisciplinary treatment of PVO. Surgery was generally indicated for PVO patients with neurologic deficit or structural instability. For PVO patients with neurologic deficit, spine surgeons decide the necessity of emergency surgery after surgical risk assessment by emergency medical consultation. However, for PVO patients with only structural instability, surgery was carefully decided by spine surgeons and infectious disease specialist according to the presence of definitely progressive pain and deformity during the treatment by the following protocol. Initial diagnostic approach for microbiological isolation included computed tomography guided biopsy and blood culture, and patients with negative results underwent surgical transpedicular biopsy. Antibiotic regimen and duration of antibiotics were routinely determined by infectious disease specialists, based on the laboratory results including culture study. All patients received intravenous antibiotics for at least 6 weeks according to the laboratory and clinical findings. Immobilization by rigid orthosis was done for about 3 months until complete infection healing. Individual type and duration of rigid orthosis were determined by spine surgeons, based on the clinical and radiologic findings. According to the timing of the first surgery for PVO, surgical treatment for PVO was categorized into early (within 6 weeks after diagnosis) and later surgery (>6 weeks after diagnosis)

Measurement of bone mineral density

In the spine center of our institute, measurement of BMD by dual-energy x-ray absorptiometry (DXA; QDR-4500A, Hologic, Waltham, MA, USA) was routinely done for all admitted patients aged >60 years. If medications for osteoporosis are required by the result of DXA, performing follow-up DXA annually by the regulation of our national health insurance system is mandatory. If follow-up DXA was not performed after 365 days since previous DXA, their medications for osteoporosis were not permitted by our national health insurance system. Therefore, follow-up BMD could be performed in all PVO patients with osteoporosis medication, and comparison of BMD was possible for PVO patients with medications for osteoporosis.

Grouping

Bisphosphonate was generally prescribed during hospitalization (approximately within 6 weeks after PVO diagnosis) or at routine follow-up visit approximately at 3 months

after PVO diagnosis. Therefore, the interval between PVO diagnosis and initiation of bisphosphonate was expected to be non-normally distributed, and the interval was categorized into groups. PVO patients were eventually divided into three groups as follows: group A (initiation of bisphosphonate within 6 weeks after PVO diagnosis); group B (initiation of bisphosphonate between 6 weeks and 3 months after PVO diagnosis), and group C (no treatment for osteoporosis) (Fig. 1). Because of the absence of guideline for bisphosphonate treatment in PVO patients, bisphosphonate treatment was expected to be initiated randomly for our PVO cohorts during admission or at routine follow-up visits. Therefore, the sequential grouping divided by such time period was anticipated to be reliable.

Four events of interest and censoring events

We tried to evaluate the long-term effectiveness and safety of bisphosphonate for PVO based on Cox proportional hazard model, and four events of interest were determined and investigated from the medical records: (1) surgery for PVO, (2) subsequent vertebral fracture of adjacent vertebral bodies, (3) recurrence of PVO, and (4) death of patients. If the patients of groups A and B stop bisphosphonate (except for bisphosphonate drug holiday) or change to the other drugs, such cases were regarded as censored cases for survival analysis. If the patients of group C start bisphosphonate treatment after grouping, such cases were also regarded as censored cases.

Statistical analysis

Data were presented as median with interquartile range (IQR). Comparison of baseline patient characteristics among the three groups was done by the analysis of variance test or the Kruskal-Wallis test for continuous variables and the Pearson chi-square test or the linear-by-linear association for categorical variables. The Kaplan-Meier method was used to estimate the cumulative probability of each four event. The Cox proportional hazard model was used to adjust for baseline differences, and hazard ratios (HRs) for four events of interest according to the treatment groups were calculated and compared. Adjustments were done additionally for age, gender, body mass index (BMI), Charlson Comorbidity Index, severity of infection, initial CRP, duration of antibiotics, type of bisphosphonate, and BMD of total femur. For statistical analysis, SPSS version 24.0 (IBM Corp, Armonk, NY, USA) was used, and a p value $<.05$ was considered significant.

Results

Enrollment and grouping

A total of 360 PVO patients with osteoporosis (by the World Health Organization osteoporosis definition) were identified after initial exclusion (Fig. 1). Among 360 patients, 101 patients (28.0%) received bisphosphonate treatment within 6 weeks after PVO diagnosis (group A). In addition, 118 patients (32.8%) received bisphosphonate treatment between 6 weeks and 3 months after PVO diagnosis (group B), and 141 (39.2%) received no osteoporosis treatment (group C).

Patient characteristics

The median age of 360 PVO patients was 73 years (IQR 67–78), and 187 were male patients (51.9%). The median follow-up period of the PVO patients was 32 months (IQR 18–54), and it was the shortest in group C patients (group A, 39; group B, 35; and group C, 24) (Table 1).

No differences were observed in age, gender ratio, BMI, and smoking status among the three groups (Table 1). A significant difference was observed in the Charlson Comorbidity Index among the three groups ($p = .026$) (Table 1),

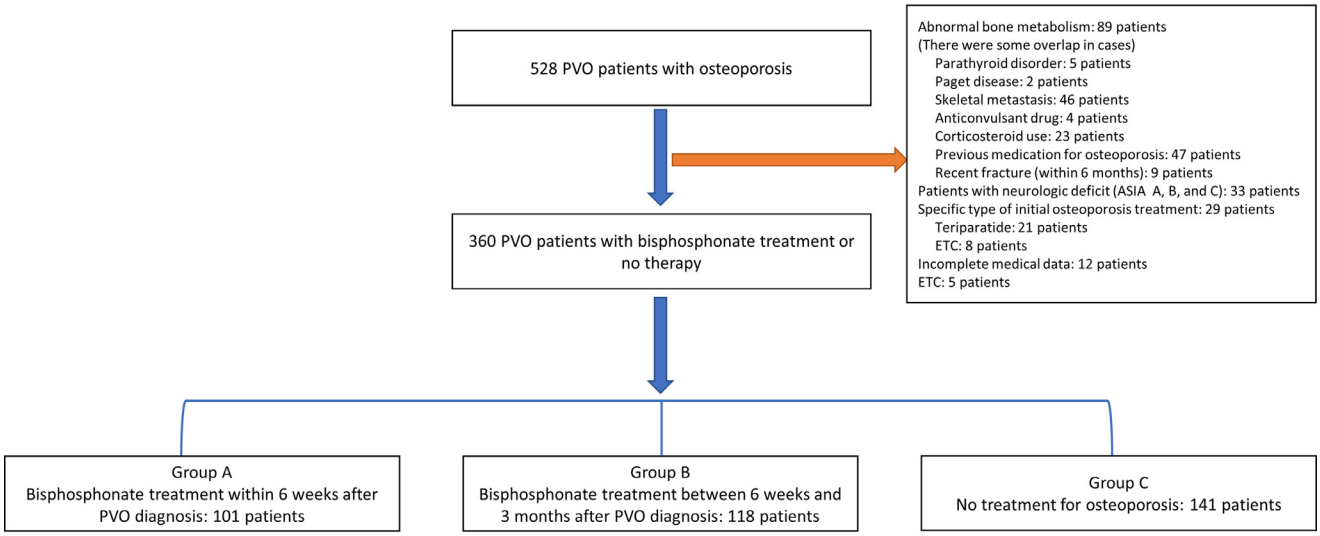

Fig. 1. Flowchart of patients included in the study. PVO, pyogenic vertebral osteomyelitis.

Table 1
Comparison of baseline characteristics among the three groups

Baseline characteristics		Group A	Group B	Group C	p Value
Definition		Bisphosphonate treatment within 6 weeks after PVO diagnosis	Bisphosphonate treatment between 6 weeks and 3 months after PVO diagnosis	No bisphosphonate treatment	
Interval between PVO diagnosis and initiation of bisphosphonate (d), median (IQR)		29 (23, 37)	66 (54, 79)		
Number of patients		101	118	141	
Follow-up period (mo), median (IQR)		39 (24, 51)	35 (21, 62)	24 (7, 52)	
Age, median (IQR)		73 (67, 78)	73 (66, 76)	74 (68, 78)	.700
Gender ratio (F:M)		48:53 (0.91:1)	61:57 (1.07:1)	64:77 (0.83:1)	.595
BMI (kg/m^2), median (IQR)		24.1 (22.5, 26.1)	24.4 (22.9, 26.3)	23.7 (22.4, 25.2)	.050
Charlson Comorbidity Index, median (IQR)		2.0 (1.0, 3.0)	2.0 (1.0, 2.0)	2.0 (1.0, 3.0)	.026
Smoking	Nonsmoker	64	74	89	.167
	Exit smokier	24	18	36	
	Current smokier	13	26	16	
Serum calcium (mg/dl), median (IQR)		8.9 (8.6, 9.2)	8.7 (8.5, 9.0)	8.8 (8.5, 9.1)	.351
Serum phosphate (mg/dl), median (IQR)		3.2 (2.8, 3.7)	3.4 (2.7, 3.9)	3.4 (3.0, 3.9)	.315
Serum nonspecific alkaline phosphatase (U/L), median (IQR)	97 (81, 129)	104 (81, 127)	99 (75, 120)	0.239	
Serum creatinine (mg/dl), median (IQR)		0.8 (0.6, 1.1)	0.8 (0.6, 0.9)	0.8 (0.6, 1.0)	.752
Type of bisphosphonate	Alendronate	24	16		.106
	Risedronate	52	62		
	Ibandronate	10	16		
	Pamidronate	5	15		
	Change to another bisphosphonate within follow-up period	10	9		
Baseline BMD (g/cm^2), median (IQR)	Spine (L1–L4)	0.880 (0.753, 1.041)	0.907 (0.793, 1.066)	0.905 (0.788, 1.056)	.871
	Femur neck	0.657 (0.558, 0.765)	0.678 (0.589, 0.759)	0.665 (0.593, 0.745)	.735
	Trochanter	0.562 (0.458, 0.702)	0.578 (0.477, 0.688)	0.582 (0.480, 0.682)	.805
	Total femur	0.703 (0.591, 0.863)	0.727 (0.638, 0.840)	0.724 (0.630, 0.828)	.698

IQR, interquartile range; BMD, bone mineral density; PVO, pyogenic vertebral osteomyelitis.

and group A patients had more medical comorbidity than group B patients according to the Charlson Comorbidity Index (p = .041). No differences were observed in initial serum levels of calcium, phosphonate, nonspecific alkaline phosphatase, and creatinine among the three groups (Table 1). Moreover, no differences were also observed in baseline BMD (g/cm^2) and type of bisphosphonate (p = .106) among the three groups at diagnosis (Table 1).

Comparison of infection profile among the three groups

The most common primary region of PVO was the lumbar region (61.4%, 221 of 360 patients), and PVO most commonly involved two vertebral bodies (68.1%, 245 of 360 patients) (Table 2). The most common causative organism was *Staphylococcus aureus* (52.8%, 190 of 360 patients). According to the classification by Pola et al., type C was the most common in our PVO cohort (154 patients, 42.8%), and 118 (32.8%) and 88 patients (24.4%) were classified as types A and B, respectively.

No differences were observed in primary region (p = .818), involved levels (p = .332), and causative organism (p = .151) among the three groups (Table 2). No differences were also observed in the initial CRP (p = .857), severity of infection by Pola et al. (p = .987), kyphotic angle (p = .612), duration of antibiotics (p = .962), and the number of cases with changes of antibiotics (p = .509) (Table 2).

Comparison of BMD changes between groups A and B

One-year follow-up BMD was available in 88 of 101 patients (87.1%) in group A and 103 of group B (87.3%). At 1-year after PVO diagnosis, follow-up BMD of group A was increased from baseline in three areas (+1.4% in femur

Table 2
Comparison of infection profile among the three groups

Infection profile		Group A	Group B	Group C	p Value
Primary region	Cervical	9	16	18	.818
	Thoracic	28	29	39	
	Lumbar	64	73	84	
Involved levels	1 level	6	9	17	.332
	2 level	75	78	92	
	Over 2 level	20	31	32	
Causative organism	*Staphylococcus aureus*	53	58	79	.151
	Gram-negative bacteria	11	29	25	
	Streptococcus species	16	12	19	
	Coagulase-negative staphylococci	9	13	9	
	Others	11	6	9	
Initial CRP (mg/L)		107 (94, 119)	104 (87, 119)	106 (89, 121)	.857
Severity of infection by Pola et al.	Type A	35	38	45	.987
	Type B	23	30	35	
	Type C	43	50	61	
Kyphotic angle (°)		0.1 (−7.3, 5.2)	−2.4 (−5.4, 4.9)	−1.7 (−5.5, 6)	.612
Duration of antibiotics (d)		46 (42, 56)	45 (42, 53)	44 (41, 58)	.962
Changes of antibiotics		17	24	21	.509

CRP, C-reactive protein.

neck, +2.3% in trochanter, and +1.8% in total femur), except for spine L1−L4 (−0.7% in spine L1−L4) (Table 3, Fig. 2). However, follow-up BMD decreased in all sites of group B (−1.7% for spine L1−L4, −0.5% for femur neck, −3.0% for trochanter, and −1.8% for total femur) (Table 3, Fig. 2).

There was a change in percentage at 1-year follow-up from baseline BMD compared by an independent t test between groups A and B (Table 3). Percent increase of BMD in group A was significantly larger than that in group B in the femur neck ($p<.001$), trochanter ($p<.001$), and total femur ($p<.001$). No significant difference was observed in BMD of spine L1−L4 between the two groups ($p=.219$).

Comparison of rate of surgical treatment among the three groups

Of the 360 PVO patients, 99 patients (27.5%) received more than one surgical treatment after PVO diagnosis. Surgical treatment was performed in 25 patients (24.8%) in group A, 31 patients (26.3%) in group B, and 43 patients (30.5%) in group C (Table 4). The median duration from PVO diagnosis to the first surgical treatment was 2.0 months (range 1−38). Forty-six patients (12.8%) received their first surgical treatment >6 weeks after PVO diagnosis. Later surgery was performed in 10 patients (9.9%) in group A, 12 patients (10.2%) in group B, and 24 patients (17.0%) in group C (Tables 4 and 5), and the median duration from PVO diagnosis to first surgical treatment was 7.0 months (range 3−38).

The HRs for overall surgery were not significantly different among the three groups (Table 4, Fig. 3). However, the difference for the occurrence of later surgery was significant after adjustment for the Charlson Comorbidity Index score (model 1, $p=.030$) and even for further adjustment for age, gender, BMI, and Charlson Comorbidity Index, severity of infection, initial CRP, duration of antibiotics, type of bisphosphonate, and BMD of total femur (model 2, $p=.030$) (Table 4, Fig. 3). Group A patients had significantly lower HRs for undergoing later surgery than group C patients ($p=.014$ for model 1 and $p=.014$ for model 2) (Table 4).

Table 3
Comparison of BMD changes between groups A and B

Time points	Location	BMD (g/cm^2), median (IQR)		Percentage increase (%)		
		Group A (n=88)	Group B (n=103)	Group A (n=88)	Group B (n=103)	p Value
Baseline	Spine (L1−L4)	0.912 (0.775, 1.066)	0.904 (0.794, 1.066)			
	Femur neck	0.677 (0.563, 0.801)	0.678 (0.589, 0.758)			
	Trochanter	0.584 (0.466, 0.733)	0.585 (0.494, 0.685)			
	Total femur	0.717 (0.607, 0.899)	0.731 (0.642, 0.823)			
At 1-year follow-up	Spine (L1−L4)	0.910 (0.767, 1.069)	0.884 (0.766, 1.036)	−0.7 (−2.4, 0.8)	−1.7 (−6.1, 2.3)	.219
	Femur neck	0.676 (0.584, 0.797)	0.669 (0.592, 0.758)	1.4 (−2.2, 4.1)	−0.5 (−2.8, 1.8)	<.001
	Trochanter	0.603 (0.505, 0.747)	0.570 (0.486, 0.652)	2.3 (−4.3, 9.4)	−3.0 (−9.4, 3.0)	<.001
	Total femur	0.730 (0.632, 0.901)	0.707 (0.593, 0.839)	1.8 (−1.5, 3.7)	−1.8 (−9.1, 3.3)	<.001

BMD, bone mineral density; IQR, interquartile range.

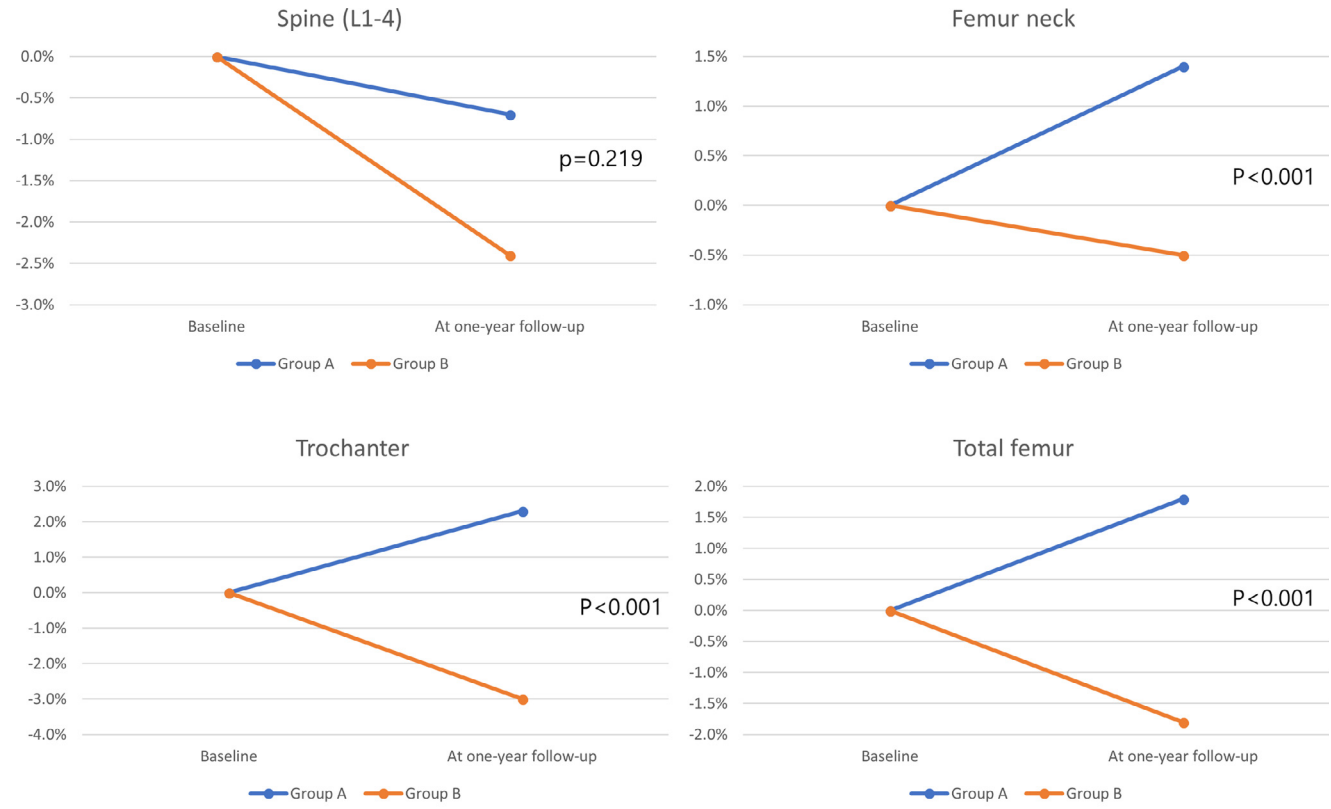

Fig. 2. Comparisons of percent changes in BMD between groups A and B at 1-year follow-up. The *Y*-axis represents mean percent change of BMD from baseline. BMD, bone mineral density.

The HRs were not significantly different between group B and group C (p = .090 for model 1 and p = .091 for model 2).

Among the three groups of patients who received later surgery, no differences or trends were found in terms of age, gender ratio, BMI, timing of surgery, kyphotic angle, and method of later surgical treatment (Table 5).

Comparison of recurrence among the three groups

Of the 360 PVO patients, 23 patients (6.4%) died before completing initial antibiotic treatment (6, 6, and 11 patients in groups A, B, and C, respectively). Of the remaining 337 patients, 30 patients (8.9%) experienced recurrence. The median time to recurrence after completing initial antibiotics treatment was 2 months (range 1–9). Recurrence occurred in 7 of 95 patients (7.4%) in group A, 9 of 112 patients (8.0%) in group B, and 14 of 130 patients in group C (Table 4).

The HRs for recurrence were not significantly different among the three groups (p = .497 for model 1 and p = .253 for model 2) (Table 4).

Comparison of subsequent fracture of adjacent vertebral bodies according to the timing of bisphosphonate

Of the 360 PVO patients, subsequent fractures occurred in 34 patients (9.4%). If the patients received surgical treatment or experienced recurrence, such cases were additionally regarded as censored cases for survival analysis. The median radiologic follow-up duration of the PVO patients were 19 months (range 1–71), and the median time from PVO diagnosis to subsequent fracture was 17 months (range 1–55) (Fig. 4). Subsequent fracture occurred in 4 patients (4.0%) in group A, 8 patients (6.8%) in group B, and 22 patients (15.6%) in group C.

The HRs for recurrence were significantly different among the three groups (p = .001 for model 1 and p = .002 for model 2), and group A and group B PVO patients had significantly lower HRs for subsequent fracture than group C (Table 4, Fig. 4).

Among the three groups of patients who experienced subsequent fracture, no differences or trends were found in age, gender ratio, BMI, timing of subsequent fracture, type of bisphosphonate, and baseline BMD (Table 6).

Comparison of survival according to the timing of bisphosphonate

Of the 360 PVO patients, 51 patients (14.2%) died after PVO diagnosis. The median duration from PVO diagnosis to death was 14 months (range 1–99). After PVO

Table 4
Hazard ratios for four events of interest according to the groups

					Model 1				Model 2			
		Group A	Group B	Group C	p Value	Group A versus group C		Group B versus group C	p Value	Group A versus group C		Group B versus group C	
		Number of patients (%)				HR with 95% CI	p Value	HR with 95% CI	p Value	HR with 95% CI	p Value	HR with 95% CI	p Value
Surgery	Overall surgery	25 (24.8)	31 (26.3)	43 (30.5)	.263	0.663 (0.404, 1.088)	.104	0.831 (0.521, 1.326)	.437	.417	0.713 (0.427, 1.190)	.196	0.832 (0.517, 1.340)	.450
	Later surgery (more than 6 weeks after diagnosis)	10 (9.9)	12 (10.2)	24 (17.0)	.030	0.396 (0.189, 0.830)	.014	0.549 (0.272, 1.109)	.090	.030	0.379 (0.175, 0.822)	.014	0.532 (0.256, 1.105)	.091
Recurrence		7 (7.4)	9 (8.0)	14 (10.8)	.497	0.578 (0.233, 1.436)	.238	0.807 (0.348, 1.871)	.617	.253	0.448 (0.170, 1.179)	.104	0.667 (0.274, 1.622)	.372
Subsequent fracture		4 (4.0)	8 (6.8)	22 (15.6)	.001	0.189 (0.065, 0.552)	.002	0.343 (0.152, 0.773)	.010	.002	0.200 (0.068, 0.595)	.004	0.321 (0.138, 0.744)	.008
Death		13 (12.9)	18 (15.3)	20 (14.2)	.468	0.669 (0.331, 1.335)	.265	0.999 (0.526, 1.896)	.996	.854	0.820 (0.397, 1.694)	.592	0.880 (0.446, 1.736)	.711

HR, hazard ratio; CI, confidence interval.
Model 1: adjusted for the Charlson Comorbidity Index.
Model 2: adjusted for age, gender, BMI, and Charlson Comorbidity Index, severity of infection, initial CRP, duration of antibiotics, type of bisphosphonate, and BMD of total femur.

diagnosis, 13 (12.9%), 18 (15.3%), and 20 (14.2%) patients died in groups A, B, and C, respectively (Table 4).

The HRs for death were not significantly different among the three groups ($p = .468$ for model 1 and $p = .854$ for model 2) (Table 4).

Discussion

Bisphosphonates theoretically prevent bone loss by inhibiting bone resorption. Numerous studies proved their effectiveness not only for osteoporosis but also for preventing bone loss caused by various diseases [36–39]. Moreover, bisphosphonate treatment showed successful inhibition of bone resorption in patients with disuse-type osteoporosis, when it was administered early after bed rest [40–42]. In this respect, early bisphosphonate treatment can be safe and helpful for preventing bone loss and improving clinical outcome in PVO patients.

PVO has not been the research area of interest to spine surgeon and infectious disease specialists. Due to such apathy, bisphosphonate treatment was almost randomly performed for our PVO cohorts in terms of initiation time (Tables 1 and 2), and no differences were found in various independent variables among the three groups. Paradoxically, the apathy about medical treatment for bone loss in PVO patients enabled our study. To the best of our knowledge, this is the first study to show the importance of early treatment for bone loss in PVO patients. Our study demonstrated that early bisphosphonate treatment (within 6 weeks after PVO diagnosis, group A) in PVO patients with osteoporosis was associated with lower occurrence of subsequent vertebral fracture of adjacent vertebral bodies. Moreover, despite similar occurrence of overall surgery, early bisphosphonate treatment was associated with lower occurrence of later surgery (>6 weeks after PVO diagnosis). Recurrence of infection and patients' survival were not significantly different according to the bisphosphonate treatment.

Considerable clinical effect of early bisphosphonate including prevention of subsequent vertebral fracture and reduction of later surgery in our PVO cohort is not surprising (Fig. 5). Direct bone loss from causative organisms is thought to be maximized in the early period before the appropriate antibiotics achieve their therapeutic concentration. Indirect bone loss from disuse and limited sunlight exposure is also thought to be maximized in the early period of initial hospitalization for the administration of about 6-week intravenous antibiotics. Moreover, our PVO cohorts are elderly (age ≥ 60 years) and osteoporotic patients with several medical comorbidities (Table 1), who already had increased thoracic kyphosis [43,44], decreased back muscle strength [43], decreased mobility, and resultant high risk of falls (Fig. 5) [45,46]. In these vulnerable osteoporotic PVO patients, a relatively small amount of bone loss can cause spinal instability and spinal sagittal malalignment at the PVO region, which induces subsequent

Table 5
Comparison of patient characteristics in patients who received later surgery

Patients' characteristics		Group A	Group B	Group C	p Value
Number of patients		10	12	24	24
Age, median (IQR)		74.0 (71.3, 78.0)	73.0 (68.8, 75.0)	76.0 (68.8, 76.0)	.095
Gender ratio (F:M)		8:2	9:3	15:9	.536
BMI, median (IQR)		24.7 (21.7, 25.9)	25.1 (23.9, 26.6)	24.2 (22.9, 25.3)	.180
Timing of later surgery	Months after PVO diagnosis, median (IQR)	9.5 (7.0, 12.8)	6.0 (4.5, 8.0)	7.5 (6.0, 12.0)	.651
Kyphotic angle (°)	At the time of PVO diagnosis, median (IQR)	−0.8 (−6.7, 5.0)	−1.4 (−4.1, 3.3)	−2.4 (−7.0, 5.3)	.867
	At the time of later surgery, median (IQR)	−14.3 (−19.6, −11.5)	−13.4 (−18.7, −10.8)	−15.5 (−21.1, −11.6)	.867
Method of later surgical treatment	Anterior	0	0	0	
	Posterior	9 (90.0%)	7 (58.3%)	17 (70.8%)	.257
	Anterior and posterior	1 (10.0%)	5 (41.7%)	7 (29.2%)	

IQR, interquartile range; BMI, body mass index; PVO, pyogenic vertebral osteomyelitis.

vertebral fracture [47] and increases the risk of surgical stabilization. Therefore, early bisphosphonate treatment might be considerably effective in our PVO cohort with osteoporosis who are vulnerable to bone loss (Fig. 5). The significant increase of BMD in group A over group B at 1-year follow-up (Fig. 2, Table 3) also strongly supports the clinical effect of early bisphosphonate.

Possible negative effect of bisphosphonate on bone healing [3,4] could not be directly assessed due to the lack of routine follow-up examination as computed tomography or MRI in our PVO cohort. Nevertheless, significantly lower rate of later surgery in early bisphosphonate group (group A) than in no treatment group shows that the negative effect of early bisphosphonate on bone healing might be insignificant (Table 3). These results are also in line with a previous report, which demonstrated positive effect of bisphosphonate on fracture healing of osteoporotic spinal fracture [7]. Rather, early bisphosphonate group showed a lower recurrence rate and longer survival than no treatment group, although they were not statistically significant (Table 3).

The main limitation of our study is its retrospective design. Causal relationship between early bisphosphonate treatment and superior outcome of PVO patients cannot be demonstrated without proper randomized

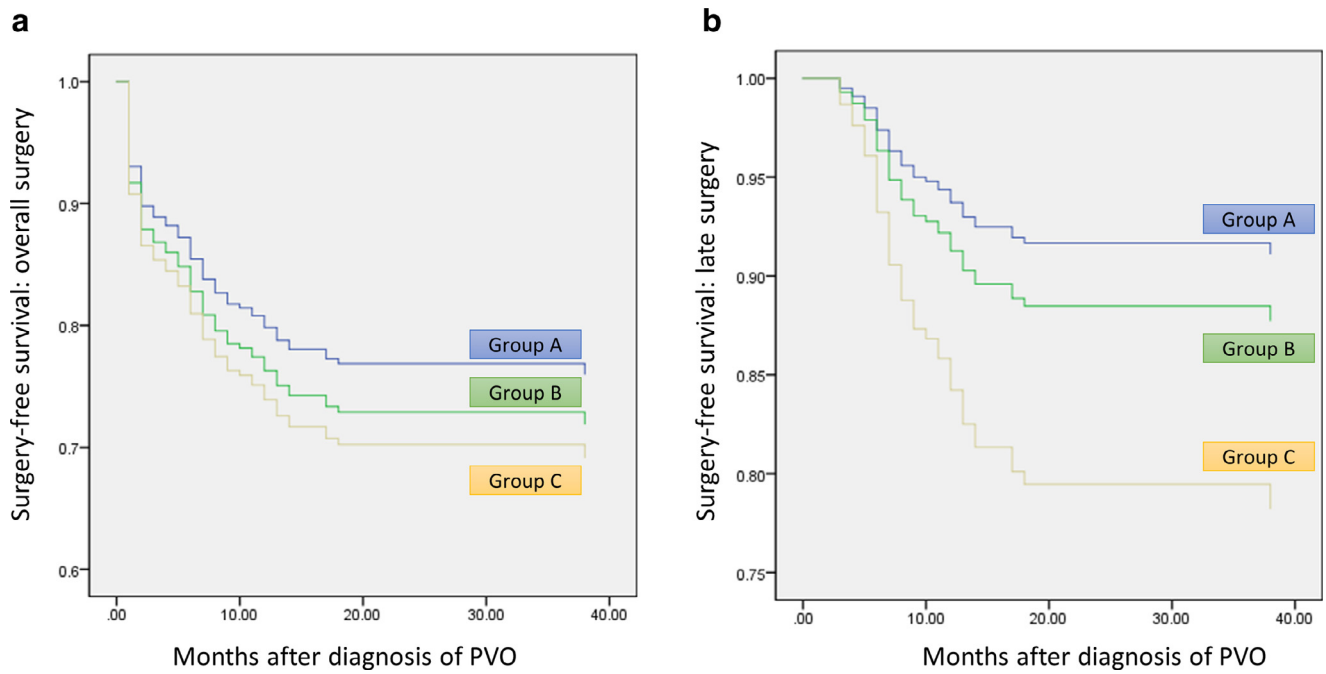

Fig. 3. Cumulative probability of surgery according to the treatment group. (Left) Surgery-free survival for overall surgery. (Right) Surgery-free survival for later surgery.

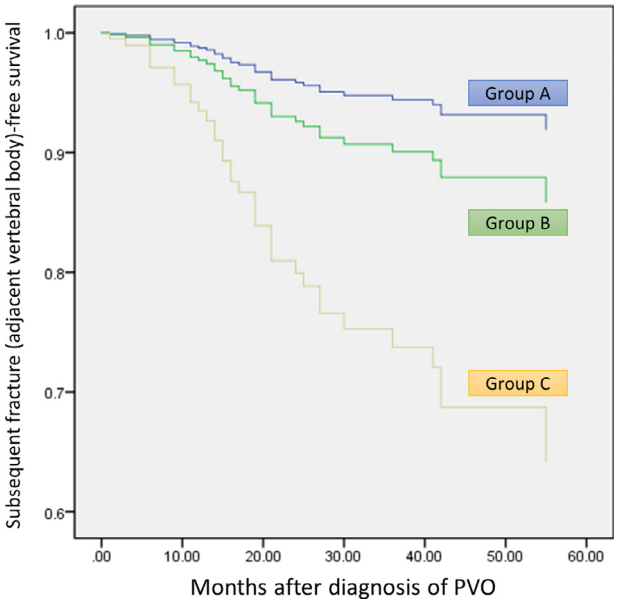

Fig. 4. Cumulative probability of subsequent fracture on adjacent vertebral bodies.

controlled studies. The gender ratio for our PVO cohort was approximately 1:1 despite male preponderance of PVO in the previous reports [19]. Due to its retrospective design, we only included PVO patients with osteoporosis, which is more common in women. In addition, it can be also worried that group C PVO cases were more severe cases of vertebral infection than group A PVO cases and that the treatment of osteoporosis in group C was not performed or delayed. We paid attention to such selection bias and tried to compare the detailed infection profile among the groups from the data available in the medical record (Table 2). Fortunately, no significant differences were observed in the infection profile among the three groups (Table 2), and our results were even significant after adjustment for several independent variables in infection profile including severity of infection by Pola et al., initial CRP, and duration of antibiotics (Table 3).

Second, comparison of BMD data was not possible with inclusion of PVO patients without bisphosphonate treatment (group C). There is no control group to identify the effect of early bisphosphonate on BMD increase, and actual effectiveness of early bisphosphonate could be doubted. Actually, it was impossible in our retrospective study because follow-up BMD could not be routinely performed in PVO patients without osteoporosis treatment. However, significant difference in BMD was even definite between early and later bisphosphonate groups (groups A and B, Fig. 2), and we expect that the early treatment group (group A) might have significant increase in BMD compared with the no treatment group (group C).

Third, the type of bisphosphonate was not consistent in our PVO cohort. Several types of bisphosphonates were used (Table 1), which could act as a strong confounding factor. Fortunately, no differences were observed in types of bisphosphonate among the three groups (Table 1), and our results were also significant even after multivariate adjustment including the type of bisphosphonate (Table 3). Finally, the superior clinical outcome of early bisphosphonate group could not be proven by comprehensive clinical scoring system such as the Oswestry Disability Index or 36-Item Short-Form Health Survey Questionnaire (SF-36). Further prospective studies, which compare clinical outcome based on validated assessment tool, are required to validate the result of our study.

In conclusion, our study demonstrated that early bisphosphonate treatment (within 6 weeks after PVO

Table 6
Comparison of patient characteristics in patients who experienced subsequent fracture

Patient characteristics		Group A	Group B	Group C	p Value
Number of patients		4	8	22	
Age, median (IQR)		74.5 (72.8, 77.3)	70.5 (63.8, 73.3)	75.0 (68.3, 77.8)	.334
Gender ratio (F:M)		2:2	5:3	16:6	.344
BMI, median (IQR)		22.3 (21.6, 23.0)	24.9 (23.1, 27.7)	23.3 (20.8, 25.1)	.252
Timing of subsequent fracture (mo), median (IQR)		21.0 (10.5, 36.3)	21.0 (13.8, 41.3)	16.5 (11.0, 21.0)	.489
Type of bisphosphonate	Alendronate	0	1		.776
	Risedronate	3	6		
	Ibandronate	1	0		
	Pamidronate	0	1		
	Change to another bisphosphonate within follow-up period	0	0		
Baseline BMD (g/cm^2), median (IQR)	Spine (L1–L4), median (IQR)	0.877 (0.778, 0.935)	0.871 (0.764, 1.124)	0.873 (0.802, 0.957)	.891
	Femur neck	0.600 (0.485, 0.674)	0.719 (0.562, 0.743)	0.638 (0.562, 0.701)	.585
	Trochanter	0.607 (0.567, 0.651)	0.634 (0.465, 0.725)	0.543 (0.495, 0.592)	.504
	Total femur	0.679 (0.599, 0.753)	0.783 (0.611, 0.845)	0.686 (0.652, 0.743)	.686

IQR, interquartile range; BMI, body mass index.

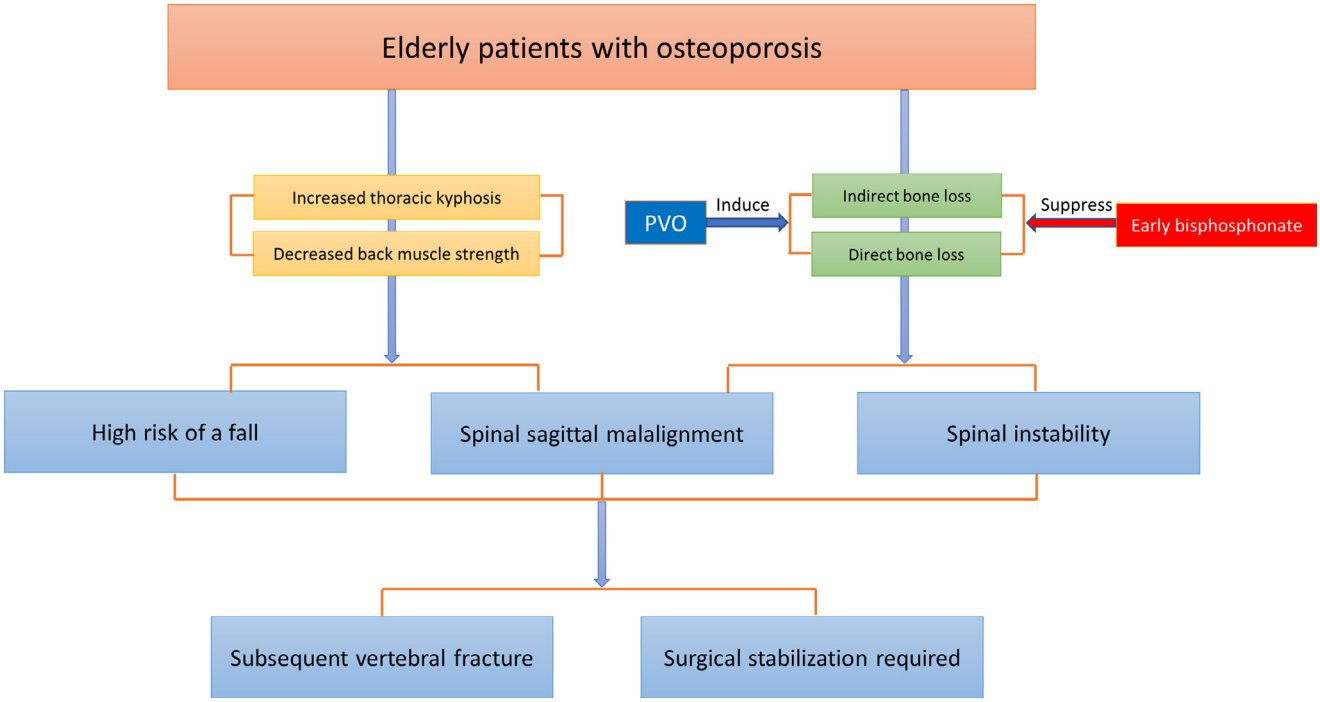

Fig. 5. Suggested mechanism for the clinical effect of early bisphosphonate on PVO patients with osteoporosis. PVO, pyogenic vertebral osteomyelitis.

diagnosis, group A) in PVO patients with osteoporosis was associated with lower occurrence of subsequent vertebral fracture of adjacent vertebral bodies and lower occurrence of later surgery (more than 6 weeks after PVO diagnosis).

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