Observational Study

Medicine

OPEN

Risk factors for new vertebral compression fracture after kyphoplasty and efficacy of osteoporosis treatment

A STROBE-compliant retrospective study

Sang Sik Choi, MD, PhD[a], Heezoo Kim, MD, PhD[a], Yoo Jin Choung, MD[a], Sung Jin Jeong, MD[a], Chung Hun Lee, MD, PhD[a,*]

Abstract

Kyphoplasty (KP) has been widely used to treat vertebral compression fractures (VCFs). However, the issue of new VCFs after KP remains controversial. Identification of risk factors for new VCF after KP may help prevent their occurrence in patients. This study aimed to retrospectively determine the major risk factors for new VCF after KP, including those associated with osteoporosis drugs used after kyphoplasty. We reviewed 117 patients who underwent single-level KP. During the follow-up period of 1 year after KP, the demographic data of these patients were compared by dividing them into two groups: those with new fractures (n = 19) and those without new fractures (n = 98). We investigated the age, sex, fracture location, medical history, steroid use history, bone mineral density (BMD), type of osteoporosis treatment, period from fracture to KP, KP method (unilateral or bilateral), bone cement dose, intradiscal cement leakage, preoperative and postoperative compression ratio, kyphotic angle (KA), and lowest vertebral body height in the fractured vertebrae. Based on these data, the factors related to new VCFs after KP were investigated using univariate and multivariate logistic regression analyses. We also investigated whether there were differences in new VCFs according to the type of osteoporosis treatment. During the 1-year follow-up period after KP, the rate of new VCFs was 16.2%. Factors related to new VCFs were BMD, intradiscal cement leakage, KA recovery rate after 1 day, and baseline height in the univariate and multivariate logistic regression analyses. The group treated with zoledronate after KP tended to show a lower frequency of developing new VCFs than the groups treated with alendronate ($P = .07$), calcium ($P = .05$), selective estrogen receptor modulator (SERM) ($P = .15$), and risendronate ($P = .02$). This study showed that for patients with new VCFs after KP, lower BMD, greater intradiscal cement leakage, greater KA recovery rate, and lower baseline vertebral height were likely risk factors for the development of new VCFs. Additionally, among the drugs used for the treatment of osteoporosis after KP, zoledronate tends to reduce the development of new VCFs compared with other bisphosphonates, SERMs, or calcium.

Abbreviations: BMD = bone mineral density, KA = kyphotic angle, KP = kyphoplasty, MRI = magnetic resonance imaging, OVCF = (osteoporotic) vertebral compression fracture, SERM = selective estrogen receptor modulator, VP = vertebroplasty.

Keywords: bisphosphonate, calcium, kyphoplasty, selective estrogen receptor modulator, vertebral compression fracture, vertebroplasty, vitamin D

1. Introduction

With an increase in the aging population and greater life expectancy of elderly people, the frequency of osteoporotic vertebral compression fractures (OVCFs) is also increasing.[1] OVCFs can cause prolonged low back pain in elderly patients, impair mobility, affect daily activities, and lead to decreased lung function, increased mortality, and reduced quality of life.[2,3]

Kyphoplasty (KP) is a widely used and minimally invasive clinical method that has been effective in providing significant pain relief in 60% to 90% of patients with OVCF.[4,5] This effect occurs immediately through the restoration of stability and strength due to spinal reinforcement.[6] However, whether such spinal reinforcement affects the pressure of the adjacent vertebral body and causes new VCFs in the surrounding area after the procedure remains controversial.[7–10] Subsequently, several randomized controlled trials and meta-analyses have reported that the frequency of new VCFs after KP is not significantly different from that of patients who receive conservative treatment after the initial fracture and that newer VCFs could be

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files]; The datasets generated during and/or analyzed during the current study are publicly available.

[a] Department of Anesthesiology and Pain Medicine, Korea University Medical Center, Guro Hospital, Seoul, Republic of Korea.

** Correspondence: Chung Hun Lee, Department of Anesthesiology and Pain Medicine, Korea University Medical Center, Guro Hospital, Gurodong Road 148, Guro-Gu, Seoul 08308, Republic of Korea (e-mail: bodlch@naver.com).*

How to cite this article: Choi SS, Kim H, Choung YJ, Jeong SJ, Lee CH. Risk factors for new vertebral compression fracture after kyphoplasty and efficacy of osteoporosis treatment: A STROBE-compliant retrospective study. Medicine 2022;101:49(e32018).

Received: 16 May 2022 / Received in final form: 4 November 2022 / Accepted: 4 November 2022

http://dx.doi.org/10.1097/MD.0000000000032018

reduced.[1,11–13] Nevertheless, it remains unclear whether new VCFs after KP are the result of KP or the spontaneous progression of osteoporosis.[1] New VCFs after KP can be influenced by patient characteristics and preoperative or intraoperative factors. Therefore, it is essential to identify risk factors that can help prevent negative patient experiences due to the development of new VCFs.

Recently, several studies have analyzed the risk factors for new VCFs after KP.[1,13–19] These include decreased bone mineral density (BMD), cement distribution, intradiscal cement leakage, vertebral height restoration, and the number of treated vertebrae. However, the results of these studies were inconclusive or contradictory. Decreased BMD is a common risk factor significantly associated with new VCFs.[1,13–16,19] To increase BMD after KP, several osteoporosis drugs such as selective estrogen receptor modulators (SERMs), calcium, and biphosphonates are used. However, previous reports have neither studied nor compared the incidence of new VCFs related to the types of osteoporosis drugs commonly administered after KP.

Therefore, the purpose of this study was to retrospectively determine the major risk factors for new VCFs after KP including those concerning the osteoporosis drugs used after KP.

2. Methods

2.1. Study design and patient selection

This retrospective observational study adhered to the STROBE checklist (S1 checklist) and was approved by the institutional review board (2020GR0415) on September 9, 2020.

We analyzed patients who underwent KP for VCFs of the thoracic and lumbar vertebrae (T5–L5) between January 2010 and August 2019. The inclusion criteria were diagnosis of an acute or subacute fracture due to the presence of bone marrow edema on magnetic resonance imaging (MRI) before KP, a numeric rating scale pain score ≥ 4 despite conservative drug treatment after VCF, having undergone KP for a single-level VCF between T5 and L5, a BMD ≤ –2.5, and completion of the follow-up period of 12 months (regularly) after KP. The exclusion criteria were edematous fracture not seen on MRI, VCF found to be a pathological fracture due to multiple myeloma or tumor, traumatic VCF rather than VCF (BMD < –2.5), multilevel KP or vertebroplasty (VP) for multiple fractures, neurological deficits or spinal stenosis, systemic or local spinal infection before and after KP, loss to follow-up within 12-months of KP, and incomplete medical data.

Among the patients included in the analysis, those with and without a new VCF within a year after KP were divided into the "new fracture" and "no fracture" groups, respectively. The inclusion criteria for new VCFs were: 1) an apparent pain-free interval after the initial KP, followed by recurrence of back pain; 2) evidence of new VCF on magnetic resonance imaging occurring above or below previously treated levels; and 3) requirement of additional VP or KP to relieve pain due to subsequent fractures.

Additionally, all KP procedures were performed by the same physician. All patients underwent continuous epidural catheterization near the fracture level to alleviate pain caused by the fracture and during the KP procedure and were administered 200,000 IU vitamin D (Vita D Bone INJ 1 mL, Huons Co., Ltd., Sungnam city, Kyunggi province, Korea). The vitamin injections were re-administered every 3 months.

2.2. Procedure

KP was performed according to the established techniques. The patient was placed on a table in the prone position with pads under the chest and abdomen for kyphosis correction. To control the pain during the procedure, 6 mL of 0.20% ropivacaine was administered through an epidural catheter before initiation. An aseptic dressing was applied to the treated area, and local anesthesia was induced with 1% lidocaine. Under fluoroscopy, the trocar was inserted into the fractured vertebral body through the pedicle using fluoroscopically guided unilateral or bilateral percutaneous access, and advanced into the vertebral body. Following guidewire insertion, the cannula was introduced through it such that its end was positioned lateral to the posterior third of the vertebral body. A kyphoplasty balloon catheter (BALANSY balloon catheter; Han-song Biobank, Bucheon city, Kyunggi province, Korea) was inserted through the cannula and advanced two-thirds of the path into the anterior vertebral body. After the balloon was expanded to ensure simultaneous satisfactory cavities, it was deflated and the cavities were filled with polymethylmethacrylate. The procedure was stopped immediately if the cement reached the posterior quarter of the vertebrae or if the vertebrae leaked outwards.

2.3. Data collection

The following factors were investigated: age, sex, fracture location, patient medical history, history of steroid use, type of osteoporosis treatment after KP (zoledronate, alendronate, risendronate, SERMs, and calcium), period from fracture to KP, BMD, surgical method (unilateral or bilateral), bone cement dose, intradiscal cement leakage, preoperative compression ratio (Fig. 1), kyphotic angle (KA) (Fig. 2), lowest vertebral body height in the existing fractured vertebrae, postoperative compression ratio, the recovery rate of KA, and recovery rate of postoperative vertebral body height. The lowest vertebral body height before and after KP was obtained from the fractured vertebral body (Fig. 3). The recovery rate of KA and vertebral body height were expressed as (recovery of the value 1 day after kyphoplasty/baseline value) × 100 (%). Osteoporosis treatment was based on the medication or injection that the patient received before and after the KP procedure.

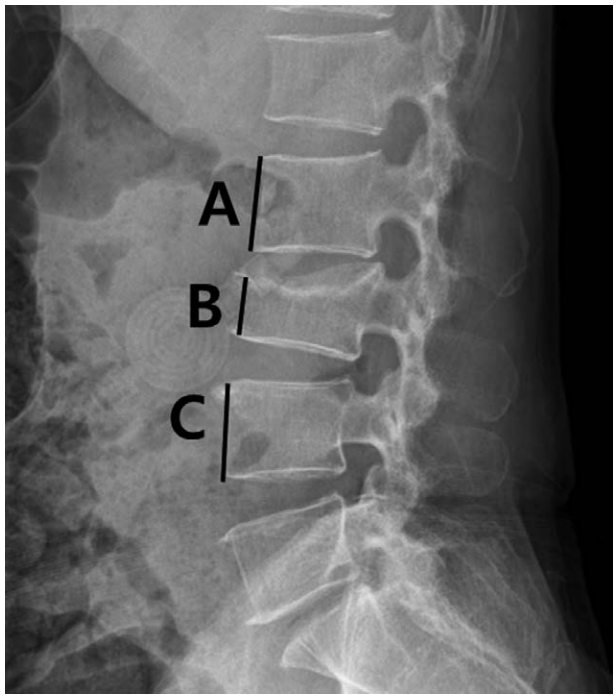

Figure 1. Measurement of vertebral compression ratio was performed using the following formula: ([A + C]/2 – B)/([A + C]/2). A: anterior vertebral height of upper vertebra, B: anterior vertebral height of fracture level, C: anterior vertebral height of the lower vertebra.

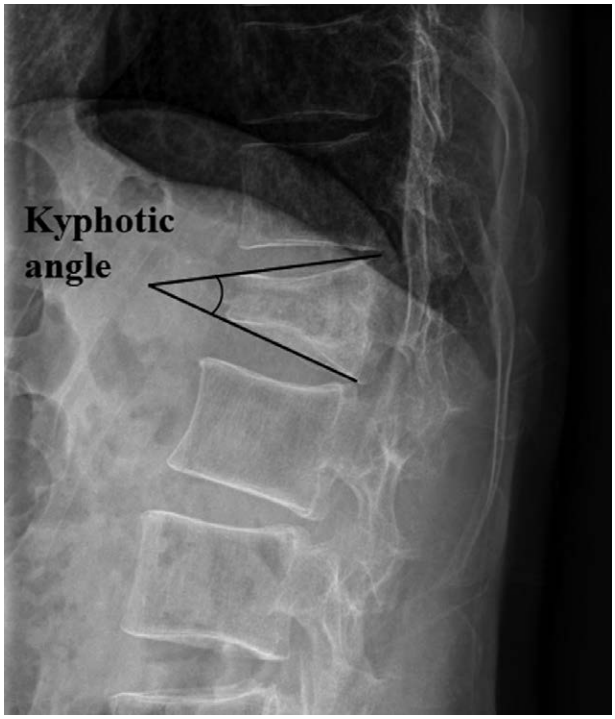

Figure 2. The kyphotic angle is calculated based on the intersection angle of the lines running parallel to the upper and lower end plates of the fractured vertebrae.

Among the characteristics of patients who satisfied the selection criteria, risk factors that were significantly related to new VCFs during the 1-year follow-up after KP were identified as the primary endpoints. Among the eligible patients, those with and without a new VCF during follow-up were divided into two groups, and the demographic data and risk factors of each group were compared to determine whether there were significant differences. The patients were classified according to the osteoporosis drugs used after KP that were used as secondary endpoints to assess whether there was a difference in the incidence of new VCFs a year after KP.

2.4. Statistical analysis

Statistical analyses were performed using SPSS version 18.0 for Windows (IBM Corp., Armonk, NY). Data are presented as mean ± standard deviation or median (interquartile range) where appropriate. Among the demographic and clinical variables between the "new fracture" and "no fracture" groups, continuous and categorical variables were analyzed using the unpaired t-test or the Mann–Whitney *U* test and the Fisher's exact test or chi-square test, respectively.

Using each risk factor (age, sex, fracture location, surgical method, medical history, history of steroid use, days from fracture to kyphoplasty, BMD, intradiscal cement leakage, bone cement dose, preoperative KA, postoperative recovery rate of KA, compression ratio, baseline vertebral height, postoperative recovery rate of vertebral height, operation time, and osteoporosis medication) as an independent variable and the occurrence of new VCFs as a dependent variable, significant items were selected using univariate logistic regression analysis. Potential risk factors for new VCFs were evaluated using multivariable logistic regression analysis by backward stepwise elimination for items found to be significantly related to new VCFs in univariate logistic regression analysis ($P < .05$, considered significant).

For each drug used after KP, the Fisher's exact test was used to compare whether there was a significant difference in the incidence of new VCF between zoledronate and other osteoporosis drugs.

3. Results

We reviewed the medical records of 225 patients. Among them, 62 patients who underwent multiple KP or VP procedures for multiple VCFs and 23 with pathological fractures resulting from cancer or metastasis were excluded. Six patients with no edema findings in the fractured vertebral body on MRI and two with post-traumatic compression fracture with a BMD > –2.5 were also excluded. In addition, three patients who died from other diseases within the follow-up period and 12 others were excluded either due to loss at follow-up or lack of necessary data for analysis. After excluding 108 patients, 117 were included in the analysis. Of these, there were 19 and 98 patients in the "new fracture" and "no fracture groups," respectively (Fig. 4).

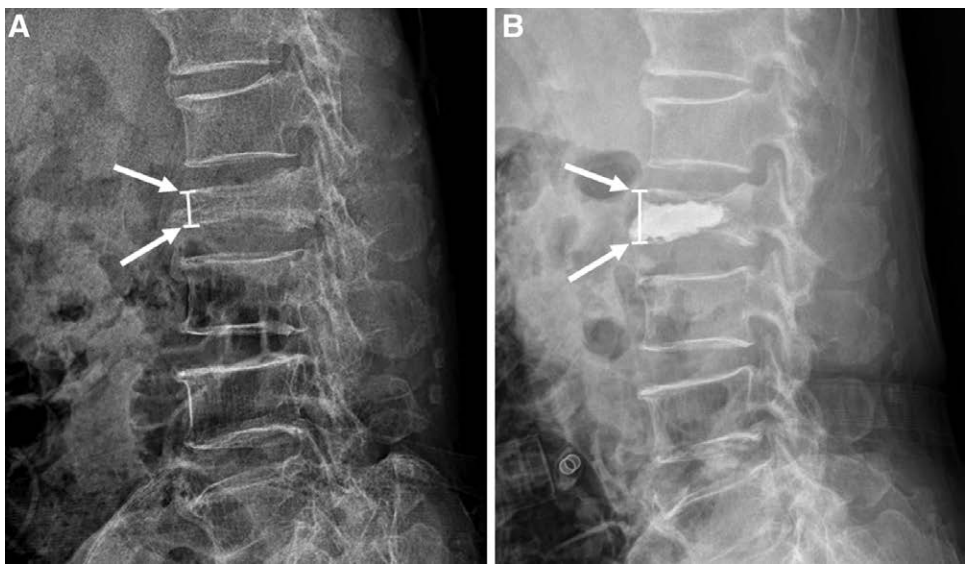

Figure 3. The level of spinal deformity was evaluated using the lowest vertebral height before and after surgery to evaluate the recovery of the vertebral height at the same location after surgery. (A) The arrow indicates the lowest vertebral height. (B) The arrow indicates the recovery of the vertebral height at the same location after surgery.

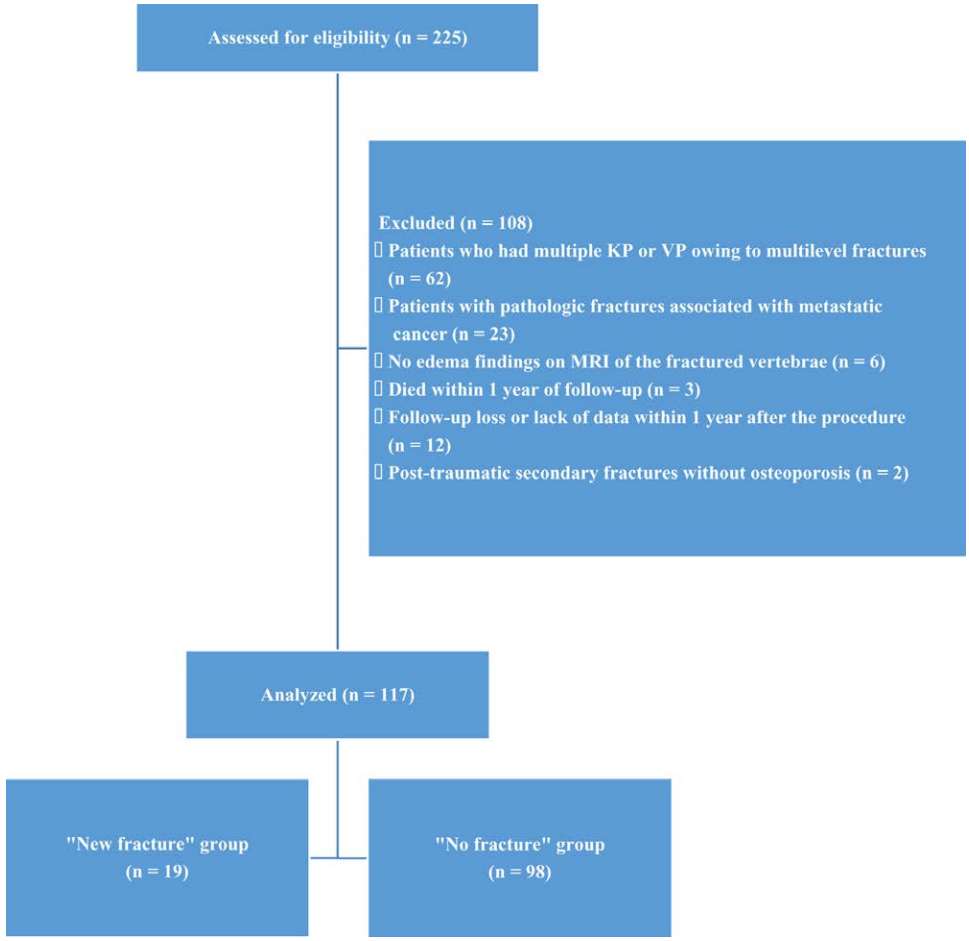

Figure 4. Flow diagram depicting the patient inclusion criteria. KP = kyphoplasty, MRI = magnetic resonance imaging, VP = vertebroplasty.

Regarding the demographic and clinical characteristics of the patients, BMD, intradiscal cement leakage, KA recovery rate after 1 day, compression ratio, baseline height, and vertebral height recovery rate after 1 day were significantly different between the two groups (Table 1). The results of univariate logistic regression analysis also showed that these parameters were significantly related to new fractures (Table 2). Multivariate logistic regression analysis showed that BMD, intradiscal cement leakage, KA recovery rate after one day, and baseline height were significantly correlated with new fractures (Fig. 5). The type of osteoporosis medication administered after KP did not show a significant correlation with new fractures in the univariate logistic analysis with significant variables. However, the group treated with zoledronate after KP showed a lower frequency of new VCFs than the groups treated with alendronate ($P = .07$), calcium ($P = .05$), and selective estrogen receptor modulators ($P = .15$). Zoledronate significantly reduced the frequency of new VCFs compared with risendronate ($P = .02$, Table 3).

4. Discussion

This study aimed to determine the risk factors that affect the occurrence of new VCFs after KP.

It assessed whether there was a significant difference in VCF incidence according to the type of osteoporosis medication used. Based on the univariate logistic regression analysis, BMD, intradiscal cement leakage, KA recovery rate after KP, compression ratio, baseline vertebral height, and vertebral height recovery rate after KP were significantly correlated with new VCFs. In multivariate logistic regression analysis of the above variables, BMD, intradiscal cement leakage, KA recovery rate, and baseline vertebral height were significantly correlated with new VCFs after KP. The type of osteoporosis medication used after KP was not significantly correlated with new VCFs. However, the zoledronate group tended to have a lower frequency of new fractures than the alendronate, calcium, and selective estrogen receptor modulator groups and had a significantly lower frequency of new VCFs than the risendronate group.

KP is considered safe and effective for the clinical treatment of VCF.[12–14] However, reports from several subsequent studies on complications related to new VCFs after KP have raised concerns regarding whether it increases the incidence of new VCFs.[7–10]

Several hypotheses have been proposed to explain the occurrence of new VCFs following KP. As cement injection into the vertebrae could theoretically induce degenerative changes in the adjacent vertebrae, the reinforced vertebrae are much harder than the adjacent vertebrae.[7,20] Furthermore, relatively hard cement implanted within the osteoporotic vertebra causes a stress peak in the end plate of the implanted vertebra, which can induce fractures at the proximal level.[21] Baroud et al[10] analyzed the biomechanical model for examining the cement buildup against the load of adjacent vertebrae and documented that the cement in the treated vertebrae acts as a pillar to reduce the physiological inward protrusion of the end plate. Thus, the pressure in the adjacent intervertebral disc increases by up to 19%, and that in the medial protrusion of the end plate adjacent to the reinforced end plate by approximately 17%, suggesting that these changes may cause adjacent fractures.

However, whether KP increases fracture rate by inducing or facilitating subsequent vertebral fractures remains controversial.

Table 1

Baseline patient characteristics.

	No fracture group (n = 98)	New fracture group (n = 19)	*P* value
Age (yr)	73.1 ± 10.3	73.1 ± 9.4	.94
Sex (M/F)	23/75	6/13	.56
Surgical method (unilateral/bilateral)	30/68	6/13	.93
Days from fracture to kyphoplasty	21.4 ± 9.2	24.2 ± 9.5	.24
Site of compression fracture	Thoracic: 39 T/L junction: 29 Lumbar: 30	Thoracic: 12 T/L junction: 5 Lumbar: 2	.11
BMD (g/cm^2)	−3.1 ± 0.7	−3.6 ± 0.8	.02
Cancer	20 (20% [13, 30%])	6 (32% [13, 57%])	.37
HTN or angina	57 (58% [48, 68%])	11 (58% [34, 80%])	.98
DM	27 (28% [19, 38%])	5 (26% [9, 51%])	.91
Asthma or COPD	13 (13% [7, 22%])	2 (10% [1, 33%])	1.0
Thyroid or parathyroid disease	10 (10% [5, 18%])	1 (5% [0, 26%])	.69
Hepatic disease	4 (4% [1, 10%])	1 (5% [0, 26%])	1.0
Kidney disease	6 (6% [2, 13%])	1 (5% [0, 26%])	1.0
Use of steroids	16 (16% [10, 25%])	6 (32% [13, 57%])	.20
Intradiscal cement leakage	11 (11% [6, 19%])	7 (37% [16, 62%])	<.001
Bone cement dose (mL)	5.3 ± 1.0	5.0 ± 1.1	.20
Preoperative KA	13.6 ± 5.2	16.5 ± 8.5	.17
Postoperative recovery rate of KA	24.6 ± 12.9	32.4 ± 14.3	.02
Compression ratio	29.8 ± 13.6	37.3 ± 17.7	.04
Baseline vertebral height	16.3 ± 4.9	12.2 ± 3.5	<.001
Postoperative recovery rate of vertebral height	17.9 ± 14.5	28.9 ± 11.8	<.001
Operation time	38.8 ± 10.6	42.8 ± 12.6	.15
Osteoporosis medication	Calcium: 24 (24% [16, 34%]) SERM: 18 (18% [11, 27%]) Alendronate: 16 (16% [10, 25%]) Risendronate: 9 (9% [4, 17%]) Zoledronate: 31 (32% [23, 42%])	Calcium: 6 (32% [13, 57%]) SERM: 4 (21% [6, 46%]) Alendronate: 4 (21% [6, 46%]) Risendronate: 4 (21% [6, 46%]) Zoledronate: 1 (5% [0, 26%])	.57 .76 .74 .22 .02
Baseline NRS score	8 (7–8)	8 (7–8)	.71

Data are presented as the mean ± standard deviation, median (interquartile range), or number (% [95% confidence interval]).

BMD = bone mineral density, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HTN = hypertension, KA = kyphotic angle, NRS = numerical rating scale, SERM = selective estrogen receptor modulator; T/L junction = thoracolumbar junction (T12–L1).

In a previous study, one vertebral body was reinforced with cement in paired osteoporotic two-vertebra functional spine units, and no cementation was applied to the control functional spine unit.[22] The authors found that the stiffness in the functional spine unit reinforced with cement did not differ from that in the control, and the breaking strength was lower than that of the control. Another study reported that the reinforcement of the vertebral body with bone cement had a very small effect on intradiscal pressure and vertebral endplate stress.[23] The researchers suggested that vertebral fractures in the adjacent vertebrae after KP were not caused by an increase in the stiffness of the treated vertebrae; instead, anterior movement of the upper body was the main associated factor. Another biomechanical study found that after treatment with KP in functional spine units, stress and strain changes were minimal in the vertebrae at the adjacent level and that these changes were within the tolerance limits for cancellous and cortical bone injuries.[24] Thus, despite biomechanical studies suggesting a plausible mechanism for an increased risk of novel fractures in vertebrae adjacent to therapeutic levels, the theory that KP induces adjacent fractures remains unclear.

When a patient experiences a VCF, the risk of developing another one increases significantly.[23–25] Lindsay et al reported that the population with an initial VCF is at a five-fold higher risk of developing additional ones than the population without VCFs.[25] They also reported that the incidence of subsequent VCFs within a year of the initial fracture was 19.2% in the absence of any surgical intervention, despite patients receiving calcium and vitamin D supplements following VCF.[25,26] This is higher than the incidence of new VCFs (16.2%) during the 1-year follow-up after KP in this study.

The reported frequency of new VCFs after kyphoplasty varies from 1% to 26%.[26,27] A direct comparison between studies is difficult because of the differences in patient demographic data, treatment methods, and follow-up periods. The reported frequencies, whether they followed conservative treatment or KP after initial VCF, underscore the need for treatment to reduce the risk of further fractures. In particular, it is important to identify variables that increase the risk of new VCFs when designing strategies to minimize risk. Therefore, in the present study, we sought ways to reduce fractures by analyzing the relationship between VCFs and risk factors and between osteoporosis drugs and newly developed VCFs.

In several previous reports, intradiscal cement leakage has been reported as a risk factor for new VCFs.[22,28–30] Owing to this, the pressure on the intervertebral disc itself increases, thereby reducing the mobility of the vertebral joint by deflecting the treated vertebral disc toward the untreated adjacent vertebra.[10,21] Moreover, an increase in the vertebral height due to intradiscal injection of cement increases this risk by increasing the weight borne by the adjacent vertebrae or by causing biomechanical changes in the distant segment if the adjacent segment is rigid.[31] However, a retrospective study wherein KP was performed using an average of 3.56 to 3.69 mL of cement reported

Table 2

Univariate logistic regression analysis results.

Risk factors	Significance	OR	OR 95% confidence interval	
			Lower limit	Upper limit
Age (yr)	.94	1.00	0.95	1.06
Sex (M/F)	.46	1.51	0.51	4.41
Surgical method (unilateral/bilateral)	.93	0.96	0.33	2.76
Days from fracture to KP	.24	1.03	0.98	1.09
Site of compression fracture				
(1) Thoracic	.14			
(2) T/L junction	.32	0.56	0.18	1.77
(3) Lumbar	.06	0.22	0.15	1.04
BMD (g/cm^2)	.01	0.43	0.22	0.84
Cancer	.29	1.80	0.61	5.33
HTN or angina	.98	0.99	0.37	2.68
DM	.91	0.94	0.31	2.86
Asthma or COPD	.74	0.77	0.16	3.72
Thyroid or parathyroid disease	.51	0.49	0.06	4.06
Hepatic disease	.82	1.31	0.14	12.37
Kidney disease	.89	0.85	0.10	7.51
Use of steroids	.13	2.37	0.78	7.15
Intradiscal cement leakage	.01	4.61	1.50	14.19
Bone cement dose (mL)	.20	0.74	0.47	1.17
Preoperative KA	.06	1.08	0.99	1.16
Postoperative recovery rate of KA	.02	1.04	1.01	1.08
Compression ratio	.05	24.85	1.04	592.33
Baseline vertebral height	<.001	0.82	0.73	0.93
Postoperative recovery rate of vertebral height	.01	1.05	1.01	1.08
Operation time	.15	1.03	0.99	1.08
Osteoporosis medication				
(1) Zoledronate	.29			
(2) Calcium	.07	7.50	0.87	68.77
(3) SERM	.10	6.89	0.71	66.48
(4) Alendronate	.08	7.75	0.79	75.23
(5) Risendronate	.03	13.78	1.36	139.30

Data were analyzed using multivariate logistic regression analysis. Adjustments were made for age, sex, time from fracture to kyphoplasty, location of the compression fracture, bone mineral density, cancer, hypertension or angina, diabetes mellitus, asthma or chronic obstructive pulmonary disease, thyroid or parathyroid disease, hepatic disease, kidney disease, steroid use, and compression ratio.

BMD = bone mineral density, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HTN = hypertension, KA = kyphotic angle, KP = kyphoplasty, OR = odds ratio, SERM = selective estrogen receptor modulator; T/L junction = thoracolumbar junction (T12–L1).

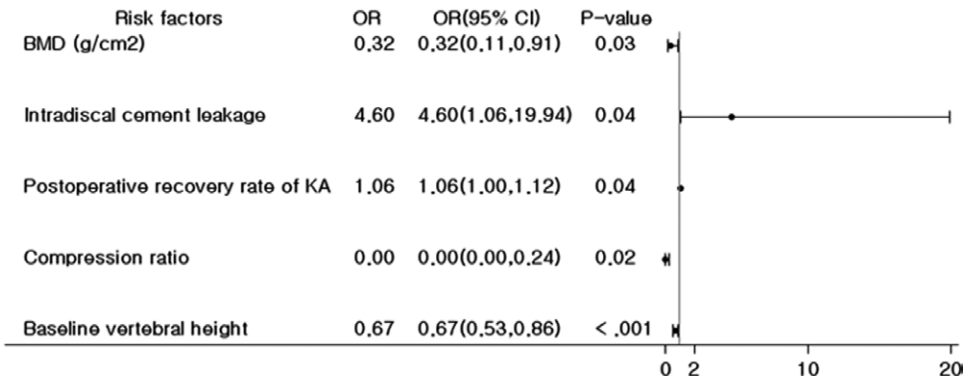

Figure 5. Results of the multivariate logistic regression analysis. Data were analyzed using multivariate logistic regression analysis. Adjustments were made for age, sex, time from fracture to kyphoplasty, location of the compression fracture, bone mineral density, cancer, hypertension or angina, diabetes mellitus, asthma or chronic obstructive pulmonary disease, thyroid or parathyroid disease, hepatic disease, kidney disease, steroid use, and compression ratio. BMD = bone mineral density, CI= confidence interval, KA = kyphotic angle, OR = odds ratio.

that intradiscal cement leakage did not significantly increase the number of vertebral fractures.[15] This result differs from those of other studies that reported intradiscal cement leakage as a risk factor for new VCFs when the average cement content ranged between 5.5 and 8.8 mL.[22,28–30] In this study, cement leakage into the disc was significantly correlated ($P < .05$) with new VCFs in both univariate and multivariate analyses when 5.28 mL of average cement was used. Therefore, we showed that cement leakage into the disc was a risk factor for new VCFs following KP when the minimum average amount of cement used was > 5.28 mL. To minimize this risk, it is recommended to inject cement as evenly as possible into the vertebral bone.[32] It is also advisable to immediately stop the injection once leakage is suspected during the procedure.[32]

The cement volume should also be considered for new VCFs. Although large amounts of cement can fill the voids of the vertebral body, they may increase the stress on adjacent vertebral bodies, thereby increasing the risk of new VCFs.[8,22] Higher rupture cases have been reported when KP was performed following the practice of maximizing cement-filling (average 9.14 mL).[8]

Table 3

Comparison of the incidence of new vertebral fractures after KP between zoledronate and other osteoporosis drugs.

				Fisher's exact test
Zoledronate	**Fx number**	**Other osteoporosis medication**	**Fx number**	***P* value**
Zoledronate (n = 31)	1 (3% [0, 17%])	Alendronate (n = 16)	4 (25% [7, 52%])	.07
		Risendronate (n = 9)	4 (44% [14, 79%])	.02
		Calcium (n = 24)	6 (25% [10, 47%])	.05
		SERM (n = 18)	4 (22% [6, 48%])	.15

Data were analyzed using the Fisher's exact test. Statistical significance was set at $P < .05$. Data are presented as numbers (% [95% confidence interval]).
Fx = fracture, KP = kyphoplasty, SERM = selective estrogen receptor modulator.

However, in studies that claimed that there was no significant relationship between the amount of cement injected and new VCFs, the average cement volume ranged between 3.56 and 5.6 mL.[13,15,18,30] In the present study, univariate analysis showed that the amount of cement injected (average 5.28 mL) did not significantly correlate with new VCFs. In addition, according to Martinčič et al,[33] filling up to 15% of the volume of the vertebral body with cement did not increase the compressive stiffness of the intradiscal pressure and concluded that it was appropriate to inject an average of 4 to 6 mL of cement into the thoracolumbar vertebra. Therefore, we recommend 4 to 6 mL as the appropriate injection volume as it relieves pain and does not increase the occurrence of new VCFs after KP.

Kim et al[34] suggested that the greater the degree of height restoration after cement injection into the vertebral body, the higher the risk of new VCFs. When the height of the compressed vertebra increases, the soft tissue tension around other vertebrae may increase which may in turn intensify the load on the adjacent vertebrae.[16,30] Additionally, vertebral height restoration could result in a new remote VCF due to the dynamic hammer effect in the same mechanism as intradiscal cement leakage.[30] In the present study, the recovery rate of spine height showed a significant correlation in the univariate analysis but not in the multivariate analysis. However, in both univariate and multivariate analyses, the smaller the baseline vertebral height, the more significant the correlation was with the new VCF. This result is similar to the findings of Pflugmacher et al[7] who reported that the lower the height of the fractured vertebrae, the higher the stress at the adjacent level and therefore the higher the risk of subsequent fractures.

An exacerbation of kyphosis due to VCFs alters the biomechanical aspects of the vertebrae, increases anterior stress at the proximal level, and increases the risk of new VCFs in the adjacent vertebrae.[7] Based on the univariate analysis in the present study, although the baseline KA did not significantly correlate with new VCFs, the compression ratio was significantly associated; however, there was no significant correlation following multivariate analysis.

The present study showed that the greater the degree of recovery of KA, the higher is the risk of new VCFs. This was significantly different in both univariate and multivariate analyses and is consistent with previous studies by Chen et al[18] and Lin et al[35] who reported larger changes in KA after KP. However, according to other researchers, KP correction is not related to new VCFs.[36–38] For example, a meta-analysis by Zhang et al showed that there is only limited evidence supporting that KA correction minimizes the occurrence of new VCFs.[31] In other words, studies that reviewed this relationship suggest that additional research such as unified multisystem studies is needed to determine whether KA correction is related to new VCFs, as some risk factors may have been involved in each study.

Most studies that documented risk factors for new VCFs after KP included BMD.[1,13–16,19] The distribution of loads can lead to structural failure, as the normal bone remodeling cycle can be impaired in patients with osteoporosis.[35] In this study, the results of univariate and multivariate analyses showed that there was a significant correlation between new VCFs and BMD. Therefore, it is essential to initiate osteoporosis treatment before and after KP, and this is highly recommended to effectively reduce the occurrence of new VCFs.[39,40] This is in line with a study by Chen et al[14] that reported a decrease in the incidence of new VCFs in patients who received osteoporosis treatment after KP compared with those who did not (13.7% vs 18.9%).

Currently, several drugs including SERMs, calcium, vitamin D, and bisphosphonates are used to treat osteoporosis. Compared with other drugs such as SERMs (raloxifene) or calcitonin, bisphosphonates have a greater ability to reduce fractures as they decrease bone turnover and significantly increase BMD.[41] Among bisphosphonates, zoledronate has the strongest potential and is effective in treating osteoporosis.[42] Zoledronate differs from other bisphosphonates as it inhibits bone resorption leading to increased secondary mineralization and replacement of remodeled spaces or existing resorption pits.[43,44] Zoledronate is also effective in treating osteoporosis in postmenopausal women and in lowering the risk of vertebral compression fracture in men.[45] This may also apply to the selection of bisphosphonates for use after KP.

Zhang et al[46] compared proximal fractures in groups treated with and without (control) zoledronate after KP. The findings revealed that no new VCFs occurred in the group that received zoledronate (n = 50), whereas, in the control group (n = 51), six patients developed new VCFs. The differences between the two groups were statistically significant. In another study, new VCFs occurred in two of 30 patients in the group that received zoledronate after KP and in six out of 30 patients in the group that received calcium after KP; the difference was statistically significant.[47] In our study, the group treated with zoledronate after KP showed a lower trend than alendronate, calcium, and SERMs and a significantly lower frequency than risendronate for new VCFs than the groups that used other drugs. This finding suggests that the use of zoledronate after KP may be more helpful in reducing new VCFs than the use of SERMs, calcium, or other pollutants.

Multi-segmental compression fracture is an important risk factor for new VCFs.[1,16] However, in this study the inclusion of patients who underwent multi-segmental compression fracture could have led to a possible bias toward the analysis of risk factors including the amount of cement, cement leakage in the disc, and fracture location. Therefore, only patients who underwent KP for a single-level fracture were analyzed to assess the risk factors.

This study has some limitations. First, the study lacked broad representation owing to its retrospective, single-center design. Therefore, future studies are needed to overcome these limitations and provide reliable clinical data. Therefore, it would be more appropriate to conduct prospective multicenter randomized controlled studies. Second, because the majority of new VCFs occurred within a year after KP, we only performed a 1-year follow-up data analysis; however, the proportion of fractures that occurred after this period may require further analysis.

5. Conclusion

This study showed that a lower BMD, greater intradiscal cement leakage, greater KA recovery rate, and smaller baseline vertebral height were likely risk factors for new VCFs after KP. Among the drugs used to lower BMD after KP, zoledronate tended to reduce the incidence of new VCFs. Collectively, these data provide evidence for the development of optimal prophylaxis for new VCFs after KP and suggest that special attention should be paid to these risk factors. Nonetheless, further studies are warranted to evaluate the effects of these risk factors and to develop new approaches to prevent the occurrence of new VCFs.

Acknowledgments

Statistical analysis was conducted after consulting Soon Young Hwang (Korea University Medical Center, Guro Hospital), a statistical expert.
We would like to thank Editage (www.editage.co.kr) for English language editing.

Author contributions

Conceptualization: Sang Sik Choi, Chung Hun Lee.
Data curation: Sang Sik Choi, Heezoo Kim, Yoo Jin Choung, Sung Jin Jeong, Chung Hun Lee.
Formal analysis: Sung Jin Jeong, Chung Hun Lee.
Investigation: Heezoo Kim, Yoo Jin Choung, Sung Jin Jeong, Chung Hun Lee.
Methodology: Sang Sik Choi, Heezoo Kim, Yoo Jin Choung, Sung Jin Jeong, Chung Hun Lee.
Project administration: Chung Hun Lee.
Resources: Sang Sik Choi, Yoo Jin Choung, Chung Hun Lee.
Supervision: Sang Sik Choi, Heezoo Kim.
Validation: Sung Jin Jeong, Chung Hun Lee.
Visualization: Yoo Jin Choung, Chung Hun Lee.
Writing – original draft: Heezoo Kim, Yoo Jin Choung, Sung Jin Jeong, Chung Hun Lee.
Writing – review & editing: Sang Sik Choi, Heezoo Kim, Chung Hun Lee.The authors of this work have nothing to disclose.

References

[1] Zhang H, Xu C, Zhang T, et al. Does percutaneous vertebroplasty or balloon kyphoplasty for osteoporotic vertebral compression fractures increase the incidence of new vertebral fractures? A meta-analysis. Pain Physician. 2017;20:E13–28.
[2] Nishimura A, Akeda K, Kato K, et al. Osteoporosis, vertebral fractures and mortality in a Japanese rural community. Mod Rheumatol. 2014;24:840–3.
[3] Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet 2002;359:1761–7.
[4] Tan G, Li F, Zhou D, et al. Unilateral versus bilateral percutaneous balloon kyphoplasty for osteoporotic vertebral compression fractures: a systematic review of overlapping meta-analyses. Medicine (Baltim). 2018;97:e11968.
[5] Yang H, Chen L, Zheng Z, et al. Therapeutic effects analysis of percutaneous kyphoplasty for osteoporotic vertebral compression fractures: a multicentre study. J Orthop Translat. 2017;11:73–7.
[6] Niu J, Zhou H, Meng Q, et al. Factors affecting recompression of augmented vertebrae after successful percutaneous balloon kyphoplasty: a retrospective analysis. Acta Radiol. 2015;56:1380–7.
[7] Pflugmacher R, Schroeder RJ, Klostermann CK. Incidence of adjacent vertebral fractures in patients treated with balloon kyphoplasty: two years' prospective follow-up. Acta Radiol. 2006;47:830–40.
[8] Uppin AA, Hirsch JA, Centenera LV, et al. Occurrence of new vertebral body fracture after percutaneous vertebroplasty in patients with osteoporosis. Radiology. 2003;226:119–24.
[9] Lin D, Hao J, Li L, et al. Effect of bone cement volume fraction on adjacent vertebral fractures after unilateral percutaneous kyphoplasty. Clin Spine Surg. 2017;30:E270–5.
[10] Baroud G, Nemes J, Heini P, et al. Load shift of the intervertebral disc after a vertebroplasty: a finite-element study. Eur Spine J. 2003;12:421–6.
[11] Yi X, Lu H, Tian F, et al. Recompression in new levels after percutaneous vertebroplasty and kyphoplasty compared with conservative treatment. Arch Orthop Trauma Surg. 2014;134:21–30.
[12] Wardlaw D, Cummings SR, Van Meirhaeghe J, et al. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. Lancet. 2009;373:1016–24.
[13] Movrin I. Adjacent level fracture after osteoporotic vertebral compression fracture: a nonrandomized prospective study comparing balloon kyphoplasty with conservative therapy. Wien Klin Wochenschr. 2012;124:304–11.
[14] Chen Z, Chen Z, Wu Y, et al. Risk factors of secondary vertebral compression fracture after percutaneous vertebroplasty or kyphoplasty: a retrospective study of 650 patients. Med Sci Monit. 2019;25:9255–61.
[15] Ning L, Wan S, Liu C, et al. New levels of vertebral compression fractures after percutaneous kyphoplasty: retrospective analysis of styles and risk factors. Pain Physician. 2015;18:565–72.
[16] Ma X, Xing D, Ma J, et al. Risk factors for new vertebral compression fractures after percutaneous vertebroplasty: qualitative evidence synthesized from a systematic review. Spine (Phila Pa 1976). 2013;38:E713–22.
[17] Li D, Wu Y, Huang Y, et al. Risk factors of recompression of cemented vertebrae after kyphoplasty for osteoporotic vertebral compression fractures. Int Orthop. 2016;40:1285–90.
[18] Chen C, Fan P, Xie X, et al. Risk factors for cement leakage and adjacent vertebral fractures in kyphoplasty for osteoporotic vertebral fractures. Clin Spine Surg. 2020;33:E251–5.
[19] Gao C, Zong M, Wang WT, et al. Analysis of risk factors causing short-term cement leakages and long-term complications after percutaneous kyphoplasty for osteoporotic vertebral compression fractures. Acta Radiol. 2018;59:577–85.
[20] Belkoff SM, Mathis JM, Jasper LE, et al. The biomechanics of vertebroplasty. the effect of cement volume on mechanical behavior. Spine (Phila Pa 1976). 2001;26:1537–41.
[21] Polikeit A, Nolte LP, Ferguson SJ. The effect of cement augmentation on the load transfer in an osteoporotic functional spinal unit: finite-element analysis. Spine (Phila Pa 1976). 2003;28:991–6.
[22] Berlemann U, Ferguson SJ, Nolte LP, et al. Adjacent vertebral failure after vertebroplasty. A biomechanical investigation. J Bone Joint Surg Br. 2002;84:748–52.
[23] Rohlmann A, Zander T, Bergmann G. Spinal loads after osteoporotic vertebral fractures treated by vertebroplasty or kyphoplasty. Eur Spine J. 2006;15:1255–64.
[24] Villarraga ML, Bellezza AJ, Harrigan TP, et al. The biomechanical effects of kyphoplasty on treated and adjacent nontreated vertebral bodies. J Spinal Disord Tech. 2005;18:84–91.
[25] Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. JAMA. 2001;285:320–3.
[26] Fribourg D, Tang C, Sra P, et al. Incidence of subsequent vertebral fracture after kyphoplasty. Spine (Phila Pa 1976). 2004;29:2270–6; discussion 2277.
[27] Hillmeier J, Grafe I, Da Fonseca K, et al. [The evaluation of balloon kyphoplasty for osteoporotic vertebral fractures. An interdisciplinary concept]. Orthopade. 2004;33:893–904.
[28] Chen WJ, Kao YH, Yang SC, et al. Impact of cement leakage into disks on the development of adjacent vertebral compression fractures. J Spinal Disord Tech. 2010;23:35–9.
[29] Rho YJ, Choe WJ, Chun YI. Risk factors for predicting the new symptomatic vertebral compression fractures after percutaneous vertebroplasty or kyphoplasty. Eur Spine J. 2012;21:905–11.
[30] Yoo CM, Park KB, Hwang SH, et al. The analysis of patterns and risk factors of newly developed vertebral compression fractures after percutaneous vertebroplasty. J Korean Neurosurg Soc. 2012;52:339–45.
[31] Zhang Z, Fan J, Ding Q, et al. Risk factors for new osteoporotic vertebral compression fractures after vertebroplasty: a systematic review and meta-analysis. J Spinal Disord Tech. 2013;26:E150–7.
[32] Tsoumakidou G, Too CW, Koch G, et al. CIRSE Guidelines on percutaneous vertebral augmentation. Cardiovasc Intervent Radiol. 2017;40:331–42.
[33] Martinčič D, Brojan M, Kosel F, et al. Minimum cement volume for vertebroplasty. Int Orthop. 2015;39:727–33.
[34] Kim SH, Kang HS, Choi JA, et al. Risk factors of new compression fractures in adjacent vertebrae after percutaneous vertebroplasty. Acta Radiol. 2004;45:440–5.

[35] Lin WC, Cheng TT, Lee YC, et al. New vertebral osteoporotic compression fractures after percutaneous vertebroplasty: retrospective analysis of risk factors. J Vasc Interv Radiol. 2008;19:225–31.
[36] Kim MH, Lee AS, Min SH, et al. Risk factors of new compression fractures in adjacent vertebrae after percutaneous vertebroplasty. Asian Spine J. 2011;5:180–7.
[37] Lo YP, Chen WJ, Chen LH, et al. New vertebral fracture after vertebroplasty. J Trauma. 2008;65:1439–45.
[38] Lin CC, Chen IH, Yu TC, et al. New symptomatic compression fracture after percutaneous vertebroplasty at the thoracolumbar junction. AJNR Am J Neuroradiol. 2007;28:1042–5.
[39] Black DM, Thompson DE, Bauer DC, et al.; Fracture Intervention Trial. Fracture risk reduction with alendronate in women with osteoporosis: the fracture intervention trial. FIT Research Group. J Clin Endocrinol Metab. 2000;85:4118–24.
[40] Sorensen OH, Crawford GM, Mulder H, et al. Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. Bone. 2003;32:120–6.
[41] Ettinger MP. Aging bone and osteoporosis: strategies for preventing fractures in the elderly. Arch Intern Med. 2003;163:2237–46.
[42] Chen F, Dai Z, Kang Y, et al. Effects of zoledronic acid on bone fusion in osteoporotic patients after lumbar fusion. Osteoporos Int. 2016;27:1469–76.
[43] Recker RR, Delmas PD, Halse J, et al. Effects of intravenous zoledronic acid once yearly on bone remodeling and bone structure. J Bone Miner Res. 2008;23:6–16.
[44] Seeman E, Martin TJ. Co-administration of antiresorptive and anabolic Agents: a missed opportunity. J Bone Miner Res. 2015;30:753–64.
[45] Spiegel R, Nawroth PP, Kasperk C. The effect of zoledronic acid on the fracture risk in men with osteoporosis. J Endocrinol Invest. 2014;37:229–32.
[46] Zhang J, Zhang T, Xu X, et al. Zoledronic acid combined with percutaneous kyphoplasty in the treatment of osteoporotic compression fracture in a single T12 or L1 vertebral body in postmenopausal women. Osteoporos Int. 2019;30:1475–80.
[47] Huang ZF, Xiao SX, Liu K, et al. Effectiveness analysis of percutaneous kyphoplasty combined with zoledronic acid in treatment of primary osteoporotic vertebral compression fractures. Pain Physician. 2019;22:63–8.