Retrospective Review

Factors Affecting Delayed Union of Vertebral Fractures Following Percutaneous Kyphoplasty

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Background: Although percutaneous kyphoplasty (PKP) could achieve rapid pain relief for the elderly with osteoporotic vertebral compression fracture (OVCF), some patients still had risks of suffering vertebrae delayed union which led to persisting pain and vertebral collapse. Preventing the delayed vertebral union could reduce the further morbidities and medical costs for patients with OVCF after PKP.

Objectives: To explore the factors involved in delayed vertebral union after PKP in patients with OVCF.

Study Design: Retrospective analysis.

Setting: All data were from Hong-Hui hospital in Xi'an.

Methods: There were 580 patients treated using single-segment PKP between January 2011 and January 2012. Demographics, clinical data, types of vertebral fracture, and surgical data were collected to analyze the factors associated with delayed vertebral union after PKP.

Results: Twenty-nine patients (5%) experienced delayed vertebral union. Univariate analyses showed that preoperative bone mineral density (BMD), cement consumption, intravertebral cleft, restoration rate of vertebral height, and improvement in kyphotic angle were associated with delayed union of vertebrae after PKP ($P < 0.05$). Multivariate analysis revealed that preoperative BMD (odds ratio (OR) = 0.452, 95% confidence interval (CI): 0.207 – 0.987, $P = 0.046$), intravertebral cleft (OR = 9.156, 95% CI: 3.712 – 22.585, $P < 0.001$), and restoration rate of vertebral height (OR = 2.731, 95% CI: 1.622 – 4.599, $P < 0.001$) were independently associated with delayed union of vertebrae.

Limitation: A multi-center study is recommended to confirm our findings and explore the factors related to vertebrae delayed union.

Conclusions: Preoperative BMD, intravertebral cleft, and restoration rate of vertebral height could be factors independently associated with delayed union of vertebrae after PKP in patients with OVCF.

Key words: Percutaneous kyphoplasty, delayed union, osteoporotic vertebral compression fracture

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Osteoporosis is a common condition found in elderly patients and often leads to fragility fractures (1). About 17% of the elderly will suffer from incidental vertebral fractures on chest x-ray performed at the emergency department (2,3). Known risk factors for osteoporotic vertebral compression fracture (OVCF) include known osteoporosis, history of fractures, female gender, older age, Caucasian race, dementia, history of falls, inactivity, smoking, alcoholism, corticosteroids, estrogen deficiency, and vitamin D deficiency (1). Complications of OVCF include chronic back pain, back deformities, decreased pulmonary function, inactivity, low quality of life, and Kummel disease (1,4,5). OVCF is also associated with increased mortality (6,7).

OVCF may be treated using back-extensor strengthening exercises, pain control drugs, bisphosphonates, and surgery. Percutaneous kyphoplasty (PKP) is easy to perform, is minimally invasive, and achieves rapid pain relief and recovery. However, there is a risk of delayed union or nonunion. Delayed union (as defined in the patients and methods section) leads to persisting pain, vertebral collapse, and regional kyphotic deformity in patients with OVCF (8,9). Patients with failed surgeries must undergo a second surgery, leading to further morbidities and greater costs.

The factors for vertebral delayed union after PKP have not been extensively and comprehensively analyzed. A previous study showed that infections, use of steroids, radiotherapy, angiitis, pancreatitis, cirrhosis, alcoholism, atherosclerosis, and older age were risk factors for nonunion (10), all of which already being risk factors for OVCF. Another study revealed that OVCF in the thoracolumbar region, presence of a middle-column injury, and confined high intensity or diffuse low intensity on T2-weighted magnetic resonance imaging (MRI) were risk factors for delayed union in patients with OVCF (11).

Therefore, the aim of the present study was to explore the factors that may affect delayed vertebral union in patients with OVCF after PKP. This could help identify patients at higher probability of nonunion, for whom the proper approach could be taken from the beginning.

Methods

Patients

There were 580 patients with OVCF who underwent PKP between January 2011 and January 2012 at the Hong-Hui Hospital, Xi'an Jiaotong University College of Medicine, including 232 thoracic vertebrae and 348 lumbar vertebrae. There were 420 women and 160 men. The mean age was 71.9 years (range 56 – 91 years).

Inclusion criteria were 1) back pain that was exacerbated on palpation and related to the location on spinal x-ray, which showed bone marrow edema on MRI short-tau-inversion-recovery (STIR) sequences; 2) each patient had a single vertebral compression fracture without any pressure in the spinal canal; 3) osteoporosis was diagnosed based on bone density (T value ≤ -2.5); and 4) the vertebrae had full posterior vertebral wall.

Exclusion criteria were 1) more than one vertebral fracture; 2) a medical history of any PKP or vertebroplasty; 3) explosive fracture with retropulsed bone fragment in the spinal canal or neurological manifestation; 4) pathological fracture due to an old fracture or malignancy; or 5) endocrine comorbidities such as diabetes and thyroid dysfunction.

This study was approved by the medical Ethics Committee of Xi'an Jiaotong University. The committee waived the need for individual consent because of the retrospective nature of the study.

Surgical Technique

PKP was performed as per standard procedures (12). X-ray fluoroscopy was used to guide the procedure. After an incision of the skin, an 11-gauge Jamshidi needle was placed percutaneously into the posterior vertebral body through either a unilateral or bilateral transpedicular approach. A bone tamp was inserted into the fractured vertebral body, followed by inflation, and then deflation, to create a cavity for low pressure injection of polymethylmethacrylate (PMMA, Via Andrea Doria, Verona, Italy) cement and for possible height restoration. Thereafter, the inflated balloon was deflated and withdrawn, and the resulting intravertebral cavity was filled with PMMA cement, reaching the cortex of the bone. The procedure was stopped when the PMMA cement entered the posterior or external vertebral body. The needle was not removed until the cement hardened. All surgical procedures were done by the same senior surgeons.

Post-operative Treatments and Follow-up

All patients were scheduled for follow-up at one day, one month, and 3 months after PKP. X-ray and MRI (T1-weighted, T2-weighted, and STIR sequences) were used to examine the recovery of patients. The criteria for delayed union of vertebrae were any 2 of the following: 1) persistent fracture lines or absence of bony bridges shown by x-ray 3 months after operation; 2) the vertebrae without PMMA cement had low signals on T1-weighted image but high signals on T2-weighted image and STIR sequences 3 months after operation; and 3) compared with one month after surgery, scores of the visual analog scale (VAS) and Oswestry Disability Index (ODI) were increased 3 months after surgery (13).

All patients received standard treatment for osteoporosis with supplementation of calcium (1000 mg

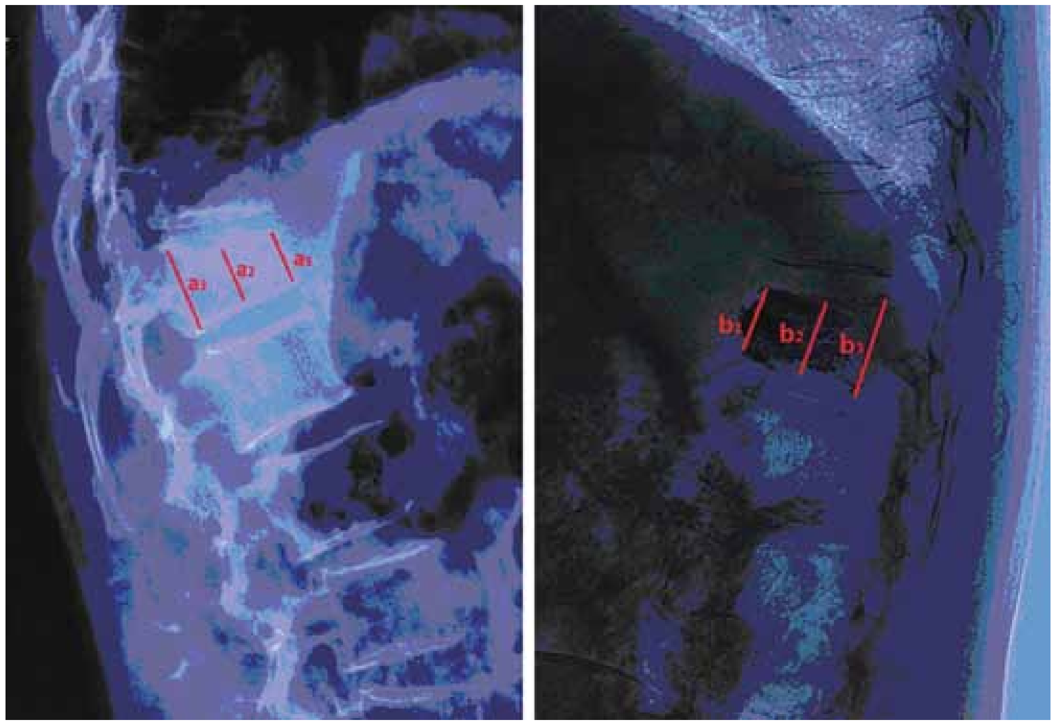

Fig. 1. *Measurement of vertebral height. The restoration rate of vertebral height was calculated as (postoperative vertebral height - preoperative vertebral height)/(predicted primary vertebral height - preoperative vertebral height)*100%.*

daily) and vitamin D (2300 IU daily). Clinical follow-up examinations were independently performed by a specialist with more than 10 years of experience. Diagnostic images were independently evaluated by a radiologist.

Data Collection

Factors that might have an influence on delayed union of vertebrae were evaluated including patients' data (gender, age, height, and weight), surgical data (surgical approach, anesthesia, PMMA cement amount, cement leakage, VAS, and ODI), and imagery data (preoperative bone mineral density (BMD), intravertebral cleft, restoration rate of vertebral height, and improvement of kyphotic angle). BMD was measured by dual x-ray absorptiometry the day before surgery. Restoration rate of vertebral height was calculated as: (postoperative vertebral height – preoperative vertebral height)/(predicted primary vertebral height – preoperative vertebral height)*100% (Fig. 1). The predicted primary vertebral height was calculated as the mean height of 2 vertebrae adjacent to the injured vertebrae.

The kyphotic angle was measured using the Cobb method (14,15) (Fig. 2). Kyphotic improvement was determined as: (preoperative Cobb angle – postoperative Cobb angle). Heights and angles were also measured by x-rays one day before surgery.

Statistical Analysis

Data were analyzed using SPSS 17.0 software (IBM, Armonk, NY, USA) and are presented as means ± standard deviation (SD). Patients with delayed union were matched (same age and gender) with patients who showed union. Both matched and unmatched analyses are presented. Factors associated with delayed union of vertebrae were explored using conditional logistics model (method: enter). Two-sided P-values < 0.05 were considered significant.

Results

Characteristics of the Patients

A total of 580 patients underwent PKP successfully. Follow-up was 7 – 24 months (mean of 16 months). Twenty-nine patients experienced delayed union in-

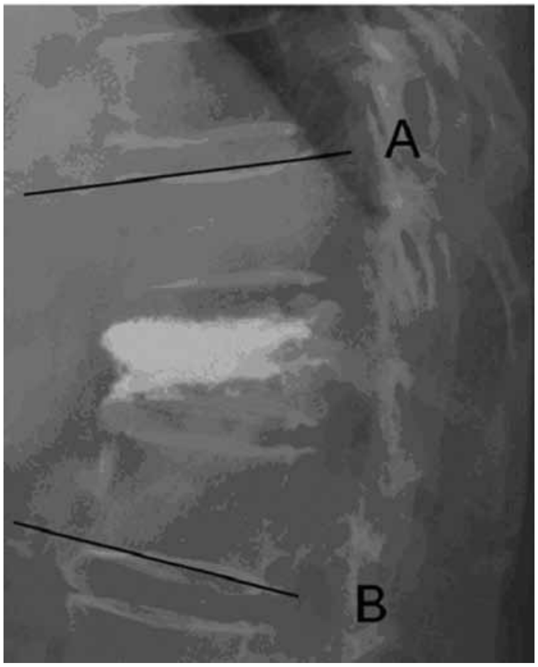

Fig. 2. *Measurement of Cobb angle. The Cobb angle was measured based on the superior endplate of the vertebra one level above the treated vertebra (line A) to the inferior endplate of the vertebral body one level below the treated vertebra (line B) on the lateral x-ray image.*

Table 1. *Characteristics of the patients (unpaired analyses).*

	Total	Delayed union	Union	*P*
	(n = 580)	(n = 29)	(n = 551)	
Gender (F)	420 (72.4%)	20 (69.0%)	359 (65.2%)	0.67
Age (years)	71.6 ± 9.7	71.7 ± 9.8	70.2 ± 8.5	0.411
Weight (kg)	56.8 ± 17.0	57.6 ± 18.3	56.7 ± 17.0	0.798
Height (cm)	152.6 ± 8.5	151.0 ± 8.0	152.6 ± 8.5	0.318
Body mass				
Index (kg / m2)	25.9 ± 6.4	26.5 ± 7.1	25.8 ± 6.4	0.567
BMD (T-score)	-2.2 ± 1.8	-3.2 ± 1.7	-2.2 ± 1.8	0.001*
Preoperative				
Vertebral height (mm)	15.4 ± 2.0	14.9 ± 2.0	15.5 ± 2.0	0.121
Predicted				
Vertebral height (mm)	16.6 ± 2.2	16.8 ± 2.6	16.6 ± 2.1	0.675

*$P < 0.05$ vs. the union group

cluding 13 with lumbar vertebrae PKP (6 L1, 5 L2, and 2 L3) and 16 with thoracic vertebrae PKP (T5, T7, T9, T10, 5 T11, and 7 T12). There was no statistically significant difference in the characteristics of the patients (gender, age, body mass index, vertebral height, and predicted vertebral height) between the 2 groups. The preoperative and predicted vertebral height were 15.2 ± 1.8 mm and 16.2 ± 2.9 mm in the union group compared with 15.6 ± 2.2 mm and 16.4 ± 3.2 mm in the delayed union group (both $P > 0.05$) (Table 1). Nine patients had delayed union among all 174 patients with PMMA leakage.

We selected 29 patients from the union group to match patients in the delayed union group (same age and gender). In the paired analyses, the amount of PMMA cement was 3.0 ± 2.5 mL in the delayed union group, which was lower than in the union group (5.1 ± 2.8 mL) (Table 2). BMD (T-score) in the delayed union group was -4.0 ± 1.9, which was worse than in the union group (-3.0 ± 2.2; $P < 0.001$). The improvement of the kyphotic improving angle and the restoration rate of vertebral height were also higher in the delayed union group (7.6 ± 4.7° vs. 4.1 ± 4.8°, $P = 0.011$; and 66% vs. 24%, $P = 0.002$, respectively). However, VAS and ODI in the union group were lower than in the delayed union group (VAS: 2.1 ± 1.0 vs. 4.1 ± 0.9, $P < 0.001$; ODI: 22.2 ± 6.9 vs. 36.2 ± 3.9, both $P < 0.001$). The presence of intravertebral cleft was significantly different: 76% in the delayed union group compared with 31% in the union group (Table 3).

Imagery findings of typical delayed and non-delayed cases are presented in Fig. 3 and Fig. 4.

Table 2. *Characteristics of the patients.*

	Total	Delayed union	Union	*P*
	(n = 58)	(n = 29)	(n = 29)	
Surgical approach				
(unilateral:bilateral)	20:38	13:16	7:22	0.097
Anesthesia				
(general:local)	22:36	10:19	12:17	0.588
Amount of PMMA	4.1 ± 2.9	3.0 ± 2.5	5.1 ± 2.8	0.002*
PMMA leakage	21 (36%)	9 (31%)	12 (41%)	0.412

*$P < 0.05$ vs. the union group

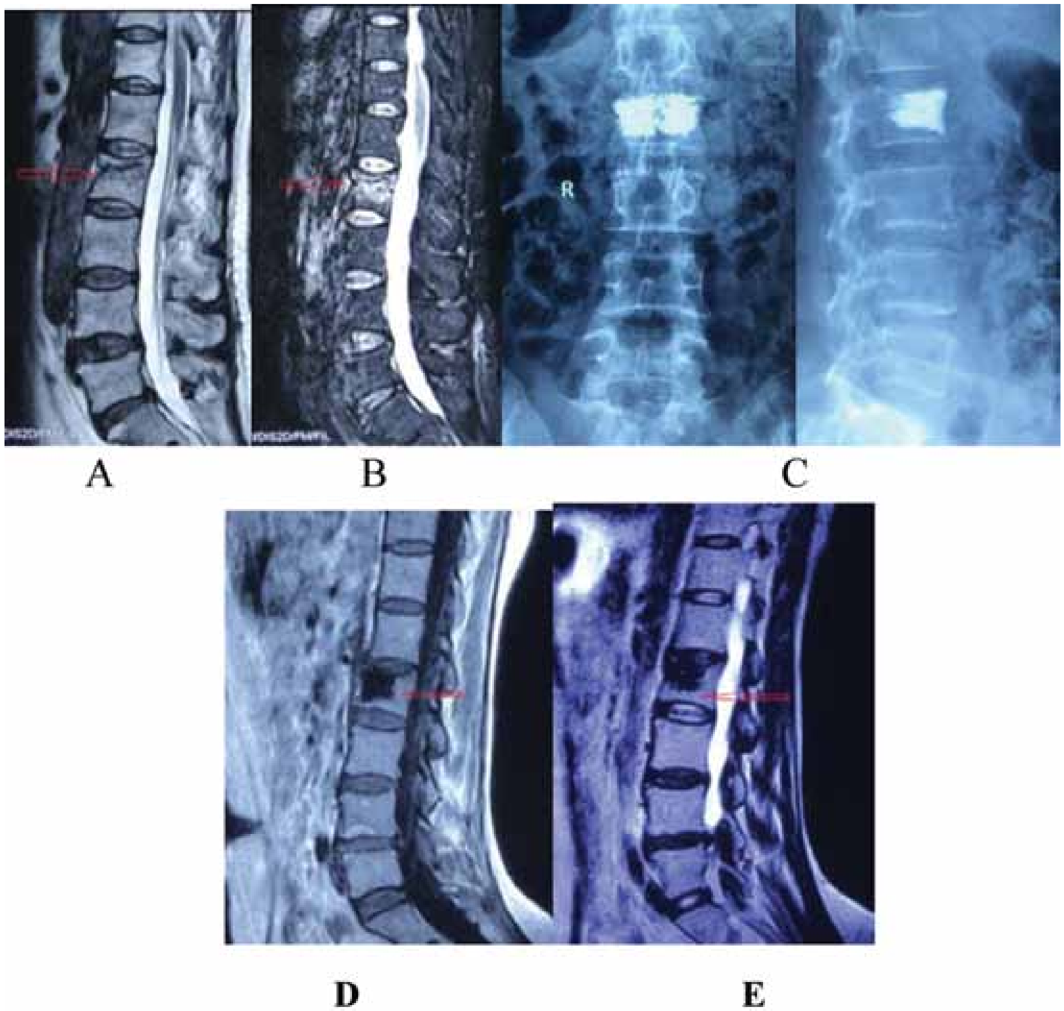

Fig. 3. *MRI of a patient with normal healing after percutaneous kyphoplasty. Female, 62-year old. (A) Low signals in the L2 vertebrae were observed in T1-weighted image (T1WI) before surgery. (B) High T2WI signals in L2 vertebrae were observed before surgery. (C) Postoperative x-ray. (D) Equisignal T1WI. (E) T2WI signals were observed between the areas outside the cement-filled of the fractured vertebrae and other no fractured vertebrae 3 months after surgery.*

Multivariate Analysis

A multivariate logistic model was used to test for factors independently associated with delayed union. Results showed that preoperative BMD (odds ratio (OR) = 0.114, 95% confidence interval (CI): 0.014 – 0.900, P = 0.039), intravertebral cleft (OR = 35.884, 95% CI: 1.690 – 762.034, P = 0.022), and restoration rate of vertebral height (OR = 4.053, 95% CI: 1.217 – 13.496, P = 0.023) were independently associated with delayed union of vertebrae (Table 4).

Table 3. *Radiological data of the patients.*

	Total	Delayed union	Union	P
	(n = 58)	(n = 29)	(n = 29)	
BMD (T-score)	-3.0 ± 2.2	-4.0 ± 1.9	-1.8 ± 1.9	< 0.001*
Intravertebral cleft	31 (53%)	22 (76%)	9 (31%)	0.001*
Restoration rate of vertebral height	26 (45%)	19 (66%)	7 (24%)	0.002*
Improvement of kyphotic angle	5.9 ± 5.0	7.6 ± 4.7	4.1 ± 4.8	0.011*
VAS	3.1 ± 1.4	4.1 ± 0.9	2.1 ± 1.0	< 0.001*
ODI	29.2 ± 9.0	36.2 ± 3.9	22.2 ± 6.9	< 0.001*

*P < 0.05 vs. the union group

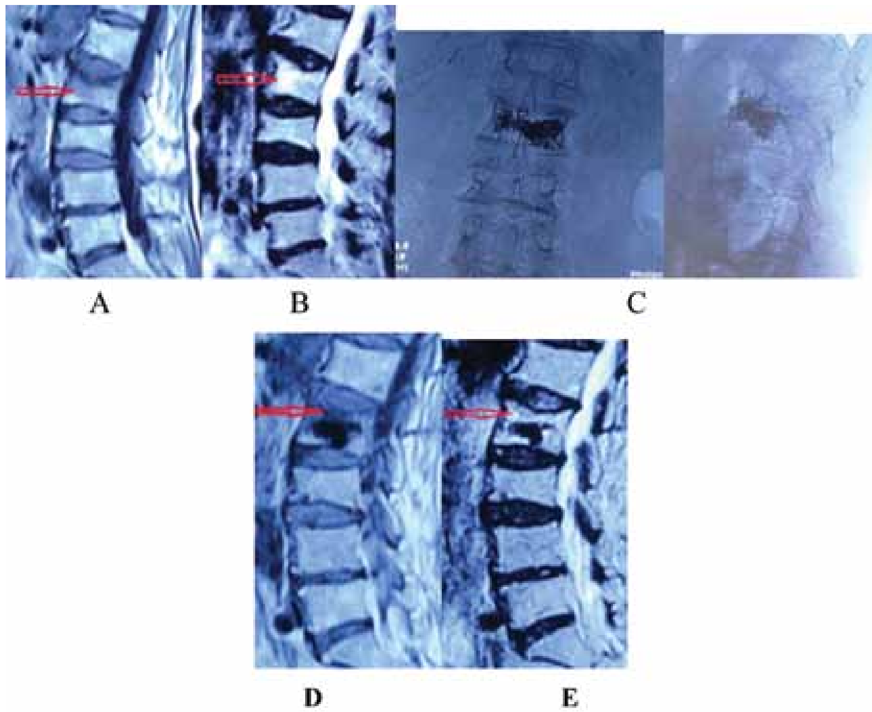

Fig. 4. *MRI of patient with delayed healing after percutaneous kyphoplasty. Female, 78-year old. (A) Low signals in the L2 vertebrae were observed in T1-weighted image (T1WI) before surgery. (B) High T2WI signals in L2 vertebrae were observed before surgery. (C) Postoperative x-ray. (D) Low T1WI signals that were different from the signals from the bone cement were observed in areas outside the cement-filled areas of the fractured vertebrae 5 months after surgery. (E) Heterogeneous high T2WI signals were observed in the areas outside the cement-filled areas of the fractured vertebrae 5 months after surgery.*

Table 4. *Multivariate analysis of the factors independently associated with non-union after PKP.*

Variable	B	SE	χ^2	*P*	OR	95% OR
BMD	-2.174	1.056	4.241	0.039	0.114	0.014 — 0.900
Amount of PMMA	0.686	0.750	0.838	0.360	1.986	0.457 — 8.636
Intravertebral cleft	3.580	1.559	5.274	0.022	35.884	1.690 — 762.034
Restoration rate of vertebral height	1.400	0.614	5.200	0.023	4.053	1.217 — 13.496
Improvement in kyphotic angle	-0.284	1.368	0.043	0.836	0.753	0.052 — 10.994

BMD was stratified according to T score of -2.5 to -3.4, -3.5 to -4.4, and < 4.5. Amount of PMMA was stratified according to < 3.0 mL, 3.0 – 4.5 mL, and > 4.5 mL. Intravertebral cleft was stratified according to present and absent. Restoration rate of vertebral height was stratified according to < 25%, 25% – 49%, 50% – 74%, > 75%. Improvement in hyphotic angle was stratified as < 3, 3 – 4.99, and > 5.

Discussion

PKP is a minimally invasive surgical treatment for OVCF and to increase the strength and stability of the vertebrae to prevent collapsing. The aim of the present study was to explore the factors that may affect delayed union after PKP in patients with OVCF. Vertebrae delayed union has a very important impact for the patients because it may determine whether they can bear weight or return to work, or whether additional surgery is required. Results showed that 29 patients (5%) experienced delayed union. Preoperative BMD, cement amount, intravertebral cleft, and restoration rate of vertebral height and kyphotic angle were associated with delayed union of vertebrae after PKP. Multivariate analysis revealed that preoperative BMD, intravertebral cleft, and restoration rate of vertebral height were independently associated with delayed union.

BMD is a common indicator used for the evaluation of osteoporosis. Previous studies showed that osteoporosis is a risk factor for new fractures. Indeed, Syed et al (14) have shown that the main reason for new fractures in 253 women who underwent vertebroplasty was osteoporosis, which is supported by other studies (16). Shiraki et al (17) consider that low BMD could induce the degeneration of vertebrae and vertebral compression factures (VCF). Fragile bone mass resulting from osteoporosis will cause new VCF. Some studies reported that osteoporosis increases the risk of new VCF after a year of vertebroplasty by 2.0 – 12.6 times (18,19). A cohort study by Lu et al (20) has shown that BMD was the only factor associated with new VCF after 2 years of follow-up ($P < 0.0001$). The occurrence of new VCF has been extensively reviewed and was termed delayed spinal degeneration, which occurs in approximately 20% of patients within one year and in 60% of areas adjacent to the augmented vertebra (21,22). However, a meta-analysis showed that there was no statistical difference between PVP and conservative treatment (23). The present study suggests that persistent osteoporosis is the primary reason for delayed union. With its development, reduction in bone mass can lead to new fractures. The bone cement cannot keep the vertebral body stiffness and strength as before. Additional studies are necessary to explore this factor.

The morbidity of OVCF with intravertebral cleft is 10% – 22% clinically (24,25), which is an important reason for persistent pain and progressive collapse of the vertebral body after conservative treatment in older patients (26). Vertebral augmentation is a safe and effective therapy for OVCF with intravertebral cleft (27). Kim and Rhyu (28) and Heo et al (29) also mention that intravertebral cleft is a key factor for recurrence after PKP. Because of intravertebral cleft, PMMA cement is often injected under a low pressure and concentrates in the cleft. If the cement does not diffuse into the intravertebral cleft effectively, the non-augmented part of the vertebrae will collapse again. Compared with diffusing cement, blocking cement not only increases local stress around cancellous bone, but also disturbs the formation of stable mechanical cross linking between cement and cancellous bone. There is persistent inching in the interface between cement and cancellous bone (30), where microfractures are often produced during daily activities.

A study by Lin et al (31) supports the present study and shows that obvious recovery in vertebral height increases the risk of secondary fractures in augmented vertebrae. Too much recovery of vertebral height may increase the tension around vertebral soft tissues and lead to an increase of stress in augmented vertebrae and their adjacent sections, and instability among vertebrae (32-34). Therefore, risks of secondary fractures in augmented vertebrae and their adjacent sections increase (31,33,34).

Continuing rupture in bone trabecula will lead to delayed union, even to serious collapses in the vertebral body and kyphotic deformity with neurological signs (35). Intravertebral clefts are common in older patients with OVCF. There are 3 main problems in performing PKP for vertebrae with intravertebral cleft. First, weak areas that are not filled with PMMA cement may continue to progress and collapse because of the cavities' irregular shapes. Secondly, cement filling will be uneven, producing uneven stress in the vertebral body. Third, compared with diffusing cement, blocking cement is less prone to form cross linking structures with cancellous bone around, which is the main reason for microfractures.

The present study is not without limitations. It was a retrospective case-control study with a small sample size. All patients were from a single hospital. Because the delayed union and union groups were very different in terms of number of patients, paired analyses had to be conducted, but pairing is never perfect and may result in bias. Multicenter studies are needed to identify the factors associated with delayed union after PKP.

Conclusions

Preoperative BMD, intravertebral cleft, and restoration rate of vertebral height are associated with delayed union of vertebrae after PKP. Low BMD, high restoration rate of vertebral height, or having an intravertebral cleft may increase the probability of delayed union.

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None

Conflict of Interest

All authors have no conflicts of interest to report.

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