

Is There a Dose–Response Relationship of Cement Volume With Cement Leakage and Pain Relief After Vertebroplasty?

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Abstract

The aim of this study was to determine if there were dose–response relationships of cement volume with cement leakage and pain relief after percutaneous vertebroplasty (PVP) for osteoporosis vertebral compression fractures (OVCFs). We collected the patient and procedural characteristics on 108 patients with OVCFs in our hospital who received PVP. Univariate and multivariate analyses were performed to explore the relationships between these potential influential variables and cement leakage and pain relief at 1 month postoperatively. Multivariate linear and logistic regression analyses were conducted with the pain score reduction and the bone cement leakage as dependent variables and the potential risk factors as independent variables, respectively. The results showed that the independent risk factors for the pain relief were the cement volume injected and fracture age, and for bone cement leakage were the cement volume injected and low-viscosity cement. In conclusion, the present study indicated that there were positive dose–response correlation relationships of cement volume with the incidence of cement leakage and the degree of pain relief after PVP, respectively. Thus, the cement should be injected into the vertebrae as much as possible during the PVP procedure.

Keywords

vertebroplasty, osteoporosis vertebral compression fracture, dose–response relationship, cement leakage, pain relief

Introduction

Since its first introduction in 1987 for the treatment of vertebral hemangioma,¹ percutaneous vertebroplasty (PVP) has been widely used for painful osteoporotic vertebral compression fractures (OVCFs), vertebral metastases, hemangioma, and myeloma and acknowledged as a gold standard treatment for painful OVCFs, with nearly 90% of patients achieving good clinical results with satisfactory pain relief.²

Accompanying with satisfying clinical efficacy after PVP, as a percutaneous minimally invasive procedure by augmenting the compressed vertebrae with injection of the bone cement, several complications associated with minimally invasive nature and bone cement leakage have been reported, including some asymptomatic minor complications or other major ones, such as nerve root injury or paralysis of patients or even death. The abovementioned complications were mainly caused by bone cement leakage either locally into the paravertebral soft tissues, the intervertebral disc, the intervertebral foramina and the spinal canal, or distally into the cardiorespiratory system causing a pulmonary embolism, with a reported incidence varying from 5% to more than 80%.³

With the benefit of PVP and major complications of bone cement leakage, early recognition of the risk factors for bone cement leakage and prompt treatment is essential to prevent devastating sequelae and make a balanced treatment decision. To date, several studies have been performed to try to reveal the risk factors for cement leakage. Some studies reported that the bone cement-related factors, including the viscosity and

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volume of the cement, were strong and independent risk factors for cement leakage,⁴⁻⁶ whereas other studies proposed that the fracture characteristics, such as the severity and type, and the surgical manner, such as unilateral or bilateral approach, were significantly associated with cement leakage.⁷⁻¹⁰ Meanwhile, results of some studies investigating the linear relationship between the cement volume and pain relief were still self-contradictory. Some studies suggested such a relationship might be present and recommended different minimum amounts of cement required to restore the vertebral stiffness and achieve satisfactory pain relief,^{4,5} although no such an association was found in others studies.

In light of this, we performed this retrospective study that included a cohort of patients with OVCFs accepting PVP by a team of spine surgeons. The purpose of this study was to analyze and determine whether there was a dose-response relationship between the cement volume and pain relief and bone cement leakage.

Material and Methods

Patients Selection

This was a retrospective study performed at our hospital and approved by the local ethics and institutional review committees (No. 2015-08-09). As the study's retrospective nature, the waiver of patients' informed consent was granted.

To reduce the confounding factors that would be introduced by including patients with multiple OVCFs, only patients with a diagnosis of subacute or acute single-level OVCF based on the presence of edema signal intensity within a compressed vertebra on the T2-weighted short-tau inversion recovery sequence magnetic resonance imaging (MRI), admitted to the Department of Orthopaedics of our hospital between April 2013 and July 2015, were included in this study. Excluded were those patients with surgery contraindications and pathologies other than osteoporosis by postoperative histopathological examination of a biopsy obtained before cement injection.

Vertebroplasty Procedure

All PVPs were performed by 1 experienced surgeon in a similar manner with biplane fluoroscopic control. Transpedicular was used in all cases with the patient in a prone position. After the pedicle of the fractured vertebra was located using the anteroposterior fluoroscopic view, local anesthetic was administered from the skin to the periosteum of the targeted pedicle. Eleven-gauge vertebroplasty needles were gently hammered into the anterior one-fourth to one-third of the vertebral body in the lateral view for unipediculate approaches, whereas placement of the needle was made into the midportion of the ipsilateral hemivertebra for bipediculate approaches. Polymethylmethacrylate (PMMA) bone cement was then injected until a homogeneous distribution of the cement was obtained or when cement leakage was noted. If cement leakage happened, the injection was terminated immediately. When necessary, a

second needle was advanced through the contralateral pedicle into the vertebral body, followed by injection of cement.

Two types of PMMA bone cement were used in this study, including low-viscosity PMMA (OsteoPal-V; Hereaus Medical, Hanau, Germany) and medium-viscosity PMMA (Spineplex; Stryker Spine, Switzerland). Cement material was prepared by combining PMMA powder with sterile barium sulfate for opacification according to the manufacturer's protocol. The cement injection was performed during the phase of "tooth-paste-like" between 4 and 8 minutes after mixing, to minimize the risks of cement leakage. Following needle removal, patients were left on strict bed rest for 1 hour until the cement reached its definitive strength. Most patients were discharged on the first day postoperatively.

Data Acquisition

Clinical characteristics on patients and diseases were obtained from the electrical medical records, including sociodemographic, procedural, and fracture data. Sociodemographic indicators included age, gender, weight, and height. Procedural data included viscosity and volume of bone cement, surgical approach (unipedicular or bipedicular). Fracture data included the level of the fractured vertebra, the percentage loss of vertebral height (fractured height/estimated prefractured height), fracture type, fracture severity grade, and fracture age (defined as the time interval between the onset of back pain related to a radiological confirmed fracture and PVP), the presence of a vertebral cleft on preoperative MRI. Vertebral height was defined as the height at the center of the vertebral body on the lateral radiograph. The height of the vertebra above the fractured vertebra was measured to estimate the prefracture height.

Fracture type (wedge, biconcave, and crush), fracture severity grade on the basis of percentage of vertebral body collapse, including mild (20%-25%), moderate (26%-40%), severe (40%-67%), and very severe (>67%) fracture, were classified according to Genant et al¹¹ and Nieuwenhuijse et al.¹²

Cement leakage was assessed on postoperative computed tomography scan of the treated levels and defined as the presence of any extravertebral cement. Patterns of cement leakage were defined using the classification proposed by Yeom et al¹³ and Tome-Bermejo et al,¹⁴ which included 4 types of leakage—(1) through the basivertebral vein (B-type), (2) through the segmental vein (S-type), (3) through a cortical defect (C-type), and (4) intradiscal leakage (D-type).

According to Prather et al's study,¹⁵ the greatest improvement of the visual analog scale (VAS) score is between the baseline score and the score at 1 month postoperatively. Thus, in this study, the degree of pain relief was defined as the difference of the VAS score between post- and preoperative average back pain with activity at 1 month postsurgery and at baseline.

The relationship between dependent variables of pain relief and bone cement leakage and independent variables of patients' and diseases' characteristics were investigated to reveal risk factors for pain relief and bone cement leakage and

to determine whether there was a dose–response relationship between the cement volume and pain relief and bone cement leakage.

Statistical Analysis

The continuous data were expressed by mean \pm standard deviation ($M \pm SD$). The Kolmogorov-Smirnov test was used to test the normal distribution of the continuous data. Independent samples Student *t* or Student-Newman-Keuls (SNK) *q* tests and Mann-Whitney *U* or Kruskal-Wallis *H* tests were used to compare the differences of pain relief and incidences of all types of bone cement leakage between different groups. Homogeneity of variance of the continuous data between different groups was verified using Levene test, before comparing the data with normal distribution and homogeneity of variance using independent samples Student *t* or SNK *q* tests between 2 or multiple groups, respectively. The categorical data were expressed as constituent ratio. Mann-Whitney *U* or Kruskal-Wallis *H* tests were used to compare the differences of the categorical data or continuous data without normal distribution between 2 or multiple groups, respectively.

Pearson and Spearman correlation analyses were used to determine the potential correlations of continuous and categorical data, respectively, to reveal the potential influential factors of the pain relief and bone cement leakage.

After exploring the potential risk factors for the pain relief and bone cement leakage using univariate analyses, multivariate regression models were performed for determining the independent risk factors for the pain relief and bone cement leakage. The validity of the regression model was tested by Hosmer-Lemeshow statistic for goodness of fit. The hazard ratio of the risk factor was expressed as regression coefficients (β) or odds ratio.

A *P* value less than .05 was considered statistically significant. All statistical tests were performed using SPSS 20 software (SPSS Inc, Chicago, Illinois).

Results

General Characteristics

A total of 108 patients with single-level OVCF were included in this retrospective study, with 65 males and 43 females. Patients improved markedly by 1 month following the vertebroplasty procedure, with the VAS score improvement from an average of 8.1 before surgery to 2.3 after surgery.

Vertebroplasty was performed between T4 and L5, including 25 thoracic vertebrae, 71 thoracolumbar vertebrae, and 12 lumbar vertebrae. A unipedicular approach was used in 71 (65.7%) patients. The presence of intravertebral clefts was found in 25 (23.1%) patients on preoperative MRI. Cement leakage was observed in 78 (72.2%) patients, including 22 (20.4%) B-type, 25 (23.1%) S-type, 17 (15.7%) C-type, and 14 (13%) D-type.

Table 1. General and Clinical Characteristics of Included Patients and PVP.

Factors	Subgroups	Value
Gender, n (%)	Male	65 (60.2)
	Female	43 (39.8)
Age: $M \pm SD$, years		67.23 \pm 9.15
Weight: $M \pm SD$, kg		74 \pm 8.41
Height: $M \pm SD$, mm		171.3 \pm 10.55
Level, n (%)	Thoracic	25 (23.1)
	Thoracolumbar	71 (65.7)
	Lumbar	12 (11.1)
Leakage type, n (%)	B-type	22 (20.4)
	S-type	25 (23.1)
	C-type	17 (15.7)
	D-type	14 (13)
Fracture severity, n (%)	Mild	25 (23.1)
	Moderate	40 (37)
	Severe	36 (33.3)
	Very severe	7 (6.5)
Fracture type	Wedge	32 (29.6)
	Crush	27 (25)
	Biconcave	24 (22.2)
	Nearly normal	25 (23.1)
Vertebral cleft, n (%)	Presence	25 (23.1)
	Absence	83 (76.9)
Approach, n (%)	Unipedicular	71 (65.7)
	Bipedicular	37 (34.3)
Cement volume, mL	Unipedicular	5.1 \pm 1.12
	Bipedicular	8.7 \pm 1.87
Cement viscosity, n (%)	Low	57 (52.8)
	Median	51 (47.2)

Abbreviations: M, mean; PVP, percutaneous vertebroplasty; SD, standard deviation.

The cement volume injected was 6.9 ± 2.1 mL, with a range of 2.5 to 12.3 mL, over all patients. Mean cement volumes were 5.1 and 8.7 mL for uni- and bipedicular approaches, respectively, and were 4.5, 7.9, and 11.2 mL for thoracic, thoracolumbar, and lumbar vertebrae, respectively.

The general and clinical characteristics are summarized in Table 1.

Univariate and Multivariate Analyses

Pearson correlation analyses showed that the factors having significant correlation with the pain relief included the female, the fracture age, the vertebral cleft present, the cement volume injected, and the thoracolumbar vertebrae. The factors having significant correlation with bone cement leakage included the vertebral cleft present, the cement volume injected, the fracture severity grade, the bipedicular approach, and the low-viscosity cement (Tables 2 and 3).

In order to find out the independent risk factors for the pain relief and bone cement leakage, multivariate linear and logistic regression analyses were conducted with the pain score reduction and the bone cement leakage as dependent variables and the factors having significant correlation as independent variables, respectively. The analysis results were shown in Table 4.

Table 2. Univariate Analyses Results of Risk Factors for Pain Relief and Cement Leakage.

Factors	Subgroups	VAS Reduction		Cement Leakage	
		M ± SD	t Test/P	n (%)	χ ² test/P
Gender	Male	5.3 ± 1.5	.004	45 (69.2)	.3935
	Female	6.1 ± 1.2		33 (76.7)	
Vertebral cleft	Presence	5.9 ± 2.15	.005	23 (92)	.0236
	Absence	4.7 ± 1.75		55 (66.3)	
Approach	Unipedicular	6.01 ± 1.22	.5822	44 (62)	.0022
	Bipedicular	5.87 ± 1.31		34 (91.9)	
Cement viscosity	Low	5.97 ± 1.42	.6853	50 (87.7)	<.001
	Median	6.11 ± 2.14		28 (54.9)	
Level	Thoracic	5.13 ± 1.15	.0036 ^a	19 (76)	.5045
	Thoracolumbar	6.52 ± 2.42		52 (73.2)	
Fracture severity	Lumbar	4.95 ± 1.02	.8397	7 (58.3)	<.001
	Mild	5.85 ± 2.37		11 (44)	
	Moderate	5.91 ± 1.75		27 (67.5)	
	Severe	6.23 ± 2.71		34 (94.4)	
Fracture type	Very severe	5.49 ± 2.93	.8677	6 (85.7)	.6547
	Wedge	6.14 ± 1.97		25 (78.1)	
	Crush	6.02 ± 2.17		16 (59.3)	
	Biconcave	5.69 ± 2.22		18 (75)	
	Nearly normal	5.78 ± 2.57		19 (76)	

Abbreviations: M, mean; SD, standard deviation; VAS, visual analog scale.

^aThe thoracolumbar subgroup is significantly different from the other 2 subgroups with regard to this factor.

Table 3. Correlation Analysis of the Factors With Pain Relief and Cement Leakage.

Factors	VAS Reduction		Cement Leakage	
	Pearson r	P	Pearson r	P
Age	−0.073	.144	0.061	.225
Fracture age	−0.39	<.001	0.054	.277
Cement volume	0.673	<.001	0.497	<.001
Level	0.078	.123	0.093	.135
Fracture severity	0.057	.244	0.341	<.001
Fracture type	0.085	.097	0.019	.457

Abbreviation: VAS, visual analog scale.

It can be shown that the independent risk factors for the pain relief only were the cement volume injected and fracture age and for bone cement leakage were the cement volume injected and the low-viscosity cement. Specifically, the risk factors for all 4 subtypes of the bone cement leakage were presented in Table 5. It can be shown that cement volume and low-viscosity cement were the most important factors having significant impact on different types and the total risk of cement leakage. Additionally, fracture severity grade and biconcave were the independent risk factors for C-type and D-type cement leakage, respectively.

Discussion

The PVP has been considered as a gold standard treatment for OVCF¹⁶ since 1989; evidence has shown that PVP can provide rapid pain relief and better function improvement than

Table 4. Multivariate Linear Regression Analyses of Risk Factors for Pain Relief.^a

Risk factors	Coefficient	t	P
Cement volume injected	35.72	13.08	<.001
Fracture age	−3.985	2.51	<.001

^aThe model: R² = 0.751, F value of 121.57, and P < .001.

conservative treatment. However, as one of the major complications of PVP, cement leakage can not only reduce the therapeutic effects of this technique but also cause some asymptomatic and other symptomatic major complications, such as nerve root injury or paralysis. Although several previous studies have commented on the optimal or minimum cement volume used in vertebroplasty, no specific threshold of cement volume was achieved to produce better pain relief efficacy. Thus, in the present retrospective, multivariate analysis of single-level PVP, we have examined the relationships between several patient- and procedure-specific factors and the clinical outcome of pain relief and cement leakage of the procedure, and we have specifically established some linear and dose–response relationships among them.

To date, only 2 studies suggested a dose–response relationship between the injected cement volume and pain relief. In Nieuwenhuijse et al's study,⁴ the authors examined the relationships between cemented vertebral body fraction and the pain relief and recommended the cement percentage fill of 24% or more for accomplishment of pain relief with postoperative VAS score less than 6 through PVP after accounting for contribution of other predictor factors using multiple logistic

Table 5. Multivariate Logistic Regression Analyses of Risk Factors for Cement Leakage.

Type	Factors	Multivariate Logistic Regression		
		OR	P	95% CI
B-type ^a	Cement volume	15.217	<.001	5.712-49.224
	Low-viscosity cement	7.767	.026	1.095-25.142
S-type ^b	Cement volume	11.712	.002	3.140-45.312
	Low-viscosity cement	2.213	.003	0.731-4.319
C-type ^c	Cement volume	5.314	.015	1.415-19.434
	Low-viscosity cement	8.111	.009	1.717-29.31
	Fracture severity grade	1.271	.029	1.106-4.521
D-type ^d	Cement volume	7.515	.004	1.775-29.611
	Low-viscosity cement	1.515	.005	0.551-7.301
	Biconcave	5.137	.031	1.02-17.001
Total ^e	Cement volume	21.540	<.001	2.511-73.617
	Low-viscosity cement	9.19	<.001	1.913-53.711

Abbreviations: B-type, basivertebral vein type; CI, confidential interval; C-type, cortical defect type; D-type, intradiscal leakage type; S-type, segmental vein type; OR, odds ratio.

^aHosmer-Lemeshow test: $P = .629$.

^bHosmer-Lemeshow test: $P = .711$.

^cHosmer-Lemeshow test: $P = .595$.

^dHosmer-Lemeshow test: $P = .409$.

^eHosmer-Lemeshow test: $P = .798$.

regression analysis. Jin et al⁵ also investigated the associations between volumetric data and clinical outcome, presence or absence of cement leakage. They concluded that a favorable outcome with postoperative pain score less than 4 could be obtained at a cement percentage fill of 11.64% or more. Both authors used the similar study methods and PVP techniques as we used but concluded inconsistent results. Thus, in the present study, we only recorded the cement volume injected rather than calculated the cement percentage fill in the vertebrae to establish its relationship with the clinical results. Ideally, this method and results could be verified and performed repeatedly by other researchers for the same population.

To determine the most influential factors for the pain relief and cement leakage, several potential risk factors found out by univariate analyses were imported into the multivariate linear and logistic regression model, respectively. The R^2 of the regression model for pain relief was 0.751 with F value of 121.57 and P value less than .001, indicating that this model could explain 75.1% of the entire variance of the risk factors impacting on the pain relief. Among these risk factors, only cement volume injected and fracture age were independent risk factors, which can significantly influence the pain relief; however, female, the vertebral cleft present, and the thoracolumbar vertebrae were all potential risk factors for the pain relief. Although Ryu et al proposed that leakage of bone cement into the epidural space could reduce the degree of pain relief expected by PVP,¹⁷ we couldn't find such a result. The possible reason might be that the injection of bone cement was terminated immediately upon occurrence of cement leakage rather than halted, continued, and terminated upon reoccurrence of cement leakage in other studies.

Meanwhile, the risk factors for cement leakage have not been identified consistently in previous studies, and the dose-response relation between cement volume and leakage was also confusing. Ryu et al found that the larger cement volume could lead to the higher incidence of epidural cement leakage.¹⁷ In Jin et al's study,⁵ the intradiscal leakage revealed a reverse dose-response relationship with cement volume at L2 to L4 levels; however, epidural leakage did not show any relationships with cement volume or percentage fill regardless of the targeted level. The smaller percentage fill less than 13% was related to a high occurrence of leakage in L2 to L4 levels. In addition, 4 operators were recruited to perform the procedure with significantly different incidences of epidural leakage in Jin et al's study. As mentioned before, the cement percentage fill is operator dependent. Thus, in the present study, only 1 doctor was recruited to perform all PVP procedures to minimize the potential confounding effects from different operators.

However, in Zhu et al's study,⁷ the risk factors for cement leakage included male, bipedicular approach, cement volume, and fracture severity. In another study, Xie et al proposed that cortical bone defects had an association with type-C cement leakage, whereas vertebrae with intact cortical bone had a higher incidence of type-S cement leakage.¹⁸ Both fracture severity and morphology were also important influential factors for cement leakage in Tome-Bermejo et al's study.¹⁴ In their study, the fracture severity had a positive correlation with D-type leakage but negative correlation with S-type leakage. Biconcave fracture exhibited higher risk of D-type leakage than wedge fracture, however, there was no such an association between wedge and crush type fractures. Lumbar and thoracolumbar vertebrae exhibited more risk of B-type leakage than thoracic vertebrae.

Besides the risk factors for the entire incidence of the bone cement leakage, the risk factors for each individual subtype of the bone cement leakage were also investigated using multivariate logistic regression analyses in the present study. It can be shown that in addition to cement volume and low-viscosity cement, fracture severity grade and biconcave fracture type were also the independent risk factors for the D-type and C-type bone cement leakage, respectively, which was concordant with previous studies.^{14,18}

The optimal timing of PVP was also conflicting. Some studies proposed that patients with fracture age more than 6 months could not benefit from the procedure,¹⁹ whereas other studies addressed that the efficacy of PVP was regardless of fracture age.^{20,21} Traditionally, PVP was limited to the patients who did not respond to 2 to 8 weeks' conservative treatment. However, early intervention was also advocated because of the low rates of the major complications related with this procedure and the possible further collapse of the fractured vertebra during the conservative treatment period.²² Thus, in our clinic, after admission, the patients with OVCF accepted the PVP as soon as possible. Our analysis results also confirmed that there was a significant negative correlation between the fracture age and the pain VAS score reduction.

The present study has several limitations. First, we didn't collect the incidences of other long-term complications of the PVP, such as the secondary vertebral fractures, or analyze their relations with the bone cement volume injected. Second, the optimal bone cement volume or percentage fill and their relations with the bone cement leakage and pain relief was not studied, which was beyond the scope of the present study. Another limitation of the present study was the small sample size with only 108 patients included.

Conclusion

The present study indicated that there were positive dose-response correlation relationships of cement volume with the incidence of cement leakage and the degree of pain relief after PVP, respectively. Thus, the cement should be injected into the vertebrae as much as possible during the PVP procedure.

Declaration of Conflicting Interests

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