Safety and Efficacy of Percutaneous Vertebroplasty for Osteoporotic Vertebral Compression Fractures: A Multicenter Retrospective Study in Japan

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─────────────── **Abstract** ───────────────

Purpose: Bone cement enhancement by percutaneous vertebroplasty (PVP) for the treatment of osteoporotic vertebral compression fractures remains unapproved, as it has not been fully evaluated in Japan. The current multicenter study was conducted in Japan to verify the safety and efficacy of PVP in patients with painful osteoporotic vertebral fractures.

Material and Methods: In this retrospective study, we referred to previous studies to evaluate the non-inferiority of PVP to balloon kyphoplasty (BKP). We reviewed consecutive patient data from April 2017 to March 2018 from four institutions based on the medical records of the intervention. We statistically investigated the adverse events due to cement leakage or other factors associated with PVP, and new vertebral compression fractures after PVP were evaluated for safety, pain relief, and gait improvement.

Results: This study included 485 patients; most of whom were in the middle- to oldest- age groups (mean age, 81.4 years). No serious adverse events were reported in patients available for safety evaluation (n = 485). Cement leakage and new vertebral compression fractures occurred in 35.7% and 18.6% (26.2%-38.4% and 8.9%-20.7%) of the patients undergoing PVP, respectively, both of which were also judged to be equivalent to those of BKP. The pain score improved in those undergoing PVP, and this improvement was maintained during a one-year follow-up. Of the 206 patients who had difficulty walking at baseline, 156 had restored walking at discharge.

Conclusions: PVP was shown to be a safe and effective treatment, even in elderly patients with painful osteoporotic vertebral fractures.

Key words: percutaneous vertebroplasty, compression fracture, osteoporosis, bone cement

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Introduction

While pain from osteoporotic vertebral compression fractures may be relieved with conservative therapy [1], previous studies have reported that pain may persist in 12%-30% of patients with osteoporotic vertebral fracture due to delayed union or subsequent pseudoarthrosis [2-5]. Severe pain

may persist for months to years, even with standard conservative therapy.

Percutaneous vertebroplasty (PVP) was first introduced in France in 1984 as a procedure for injecting bone cement for cervical vertebral hemangioma [6]. After its widespread use in Europe, PVP was introduced in the United States and implemented in several patients to treat osteoporotic vertebral fractures in the late 1990s [7-9]. PVP was subsequently approved by the Food and Drug Administration and was eventually covered by health insurance.

The safety and efficacy profiles of PVP have been reported and discussed. Of these, two multicenter randomized controlled trials (RCTs) of PVP versus a placebo procedure reported in 2009 [10, 11] demonstrated that PVP was not superior to the placebo procedure in delivering pain relief and improving the quality of life (QOL) of patients with a vertebral compression fracture. On the other hand, PVP was superior to the placebo procedure in delivering pain relief in patients within 6 weeks of the onset of the fracture after 2 weeks, and this superior efficacy was maintained for up to 6 months in an RCT reported in 2016 [12], while two subsequent RCTs did not demonstrate the superiority of PVP over placebo procedures [13, 14]. From these reports, Cochrane reviews in 2015 and its update in 2018 did not support the use of PVP in treating osteoporotic vertebral fractures in routine practice [15, 16]. However, to date, no reports are available from RCTs to show the inferiority of PVP, suggesting some roles of the procedure in providing pain relief and improving QOL. In addition, subsequent vertebral fractures are discussed. Notably, citing the small number of serious adverse events with PVP, the updated Cochrane review concluded that it remains uncertain whether PVP results in a clinically increased risk of new symptomatic vertebral fractures and/or other serious adverse events [16].

In Japan, marketing approval is yet to be given to bone cement intended for use in conjunction with PVP for the treatment of osteoporotic vertebral compression fractures. Therefore, the current multicenter retrospective study was performed in Japan to verify the safety and efficacy of PVP with the aim of obtaining manufacturing and marketing approval by the Pharmaceuticals and Medical Devices Agency.

Material and Methods

Study design

This retrospective multicenter study was approved by the institutional review board of each of the four hospitals. Written informed consent was waived for patients who received retrospective chart reviews.

The investigator in charge of each hospital approached those whose consent needed to be obtained through telephone, fully explained to them the details of the study intended, provided them with adequate opportunity to consider all options, including their freedom to withdraw consent or to participate in the study, and confirmed whether or not an informed consent form could be sent to them to complete. The investigator sent the consent form to those who had agreed to have it sent to them and had all completed forms signed and returned.

Selection of study sites

Information on the Japanese Society of Interventional Radiology (JSIR) web-based case registry list was used as a basis for choosing candidate sites for the current study, and the top four institutions on the list (hereafter referred to as institutions A, B, C, and D) were selected.

Patients

Of all patients undergoing PVP at either of the four hospitals, those who met all the inclusion criteria and none of the exclusion criteria were consecutively enrolled in the study.

Procedures

All procedures were performed by two or more radiologists, including at least one board-certified interventional radiologist who was familiar with the PVP procedure. PVP was performed in all the patients under local anesthesia using polymethyl methacrylate bone cement either Vertaplex ® (Stryker Corporation, Kalamazoo, Michigan, United States) or Simplex P ® (Stryker Corporation, Kalamazoo, Michigan, United States). The cement was injected into the vertebral body during continuous fluoroscopic screening. The injection was terminated when there was a satisfactory distribution of cement or any cement leak into the extraosseous structures.

Inclusion criteria

The inclusion criteria were as follows: 1) patients who had undergone PVP between April 2017 and March 2018; 2) those who had painful osteoporotic vertebral compression fractures that did not improve with conservative treatment; and 3) those diagnosed with bone marrow edema who had new fractures or nonunion fractures confirmed by imaging, such as magnetic resonance imaging, prior to PVP.

Exclusion criteria

The exclusion criteria were: 1) patients with severe heart diseases; 2) patients with untreatable blood coagulation abnormalities; 3) those with local or systemic infection; 4) those with pain due to musculoskeletal or muscular disease, disc herniation, or other vertebral diseases; 5) those with vertebral fractures due to vertebral hemangioma, osteoid osteoma, or malignant tumor; 6) those judged ineligible as patients for this clinical trial by the attending physician; 7) those with neurological symptoms; and 8) those who declared their unwillingness to participate in the study.

Evaluation criteria for non-inferiority of PVP to BKP

If all the patients were available for one-year follow-up, 237 or more patients were available for safety analysis, and

Table 1. Number of patients undergoing percutaneous vertebroplasty and one-year follow-up by institution

Institution	A	B	C	D	Total
No. of patients available for one-year follow-up/No. of registered patients (percentage)	183/197 (92.9%)	65/117 (55.6%)	58/88 (65.9%)	55/83 (66.3%)	361/485 (74.4%)

if the incidence of serious cement leakage-associated adverse events requiring treatment was 0 or 1 case, PVP would be judged to provide equivalent safety to that of BKP. In addition, if the rate of occurrence of cement leakage with PVP was 26.2% to 38.4%, PVP would be judged to provide equivalent safety to that of BKP (see Appendix 1).

Safety evaluation

PVP was evaluated for safety based on the following: 1) incidence of adverse events leading to health impairment associated with cement leakage or other PVP-associated factors; 2) incidence of PVP-associated cement leakage in each vertebral body; 3) incidence of adverse events, symptomatic or asymptomatic, deemed related to PVP; and 4) presence or absence of painful new vertebral compression fracture.

Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 of the Japan Clinical Oncology Group/Japan Society of Clinical Oncology version and were classified into grade 1 to 5 as follows: Grade 1: mild, asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2: moderate, minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Grade 3: severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated disabling, limiting self-care ADL. Grade 4: life-threatening consequences, urgent intervention indicated. Grade 5: adverse event-related deaths

The exact 95% confidence interval for the cement leakage rate would be 26.2-38.4%, given the cement leakage rate of 32.2% reported in 149 BKP patients. Likewise, the exact 95% confidence interval for the new vertebral compression fracture rate would be 8.9%-20.7%, given the new vertebral compression fracture rate of 14% reported in 149 BKP patients [17].

Efficacy evaluation

The efficacy of PVP was evaluated based on the following: 1) changes in the pain relief effect pre-and post-treatment, based on changes in the pain scores self-assessing back pain in each patient on a scale of 0-10 (with 0 and 10 indicating no pain and maximum imaginable pain, respectively) [10-12], known as the pain numeric rating scaling

scores and pain scores evaluated for approximately 12 months (within an evaluable range) after treatment, and recorded separately in resting and moving states; 2) changes in ambulatory ability; and 3) changes in the dose of analgesics administered over time.

Statistical analysis

Statistical analysis was performed using the Stata/MP 14.2 software (StataCorp, Texas, United States). Intragroup comparisons of non-continuous variables (changes in pain relief effect, changes in the ability to walk, and the dose of analgesics) were performed using the Wilcoxon signed-rank test, McNemar's chi-square test, or Mann-Whitney U-test. The level of significance was set at $P < 0.05$.

Results

Characteristics of eligible study registrants

From April 2017 to March 2018, patients who underwent PVP for osteoporotic vertebral body fractures were consecutively registered at the four participating institutions. A total of 485 patients were enrolled in this study. **Table 1** shows the number of patients undergoing PVP and one-year follow-up at each institution. The total number of eligible patients registered at the four institutions accounted for 85% of all registrants in Japan, thus obviating the need for retroactive patient enrollment. **Table 2** shows the clinical characteristics of the study registrants. Patients in the middle- to the oldest age group accounted for the majority (mean age, 81.4 years). **Figure 1** shows the cumulative number of pre-procedural fractures by the site of occurrence. Fractured vertebral levels ranged from the 5th thoracic vertebra to the 5th lumbar vertebra, with the 1st lumbar vertebra being the most commonly affected. Patients' data during their visit to the hospital (**Table 3**) showed that all patients had osteoporosis as a primary disease, except for two patients whose disease was unknown. The mean time from injury to hospital visit was 69.7 days (0-1,487 days), which was a relatively long period of time. Bone marrow edema was observed in most patients (441/485), and 206 of 485 patients (42.5%) had difficulty walking during the hospital visit. PVP was performed with a mean injection volume of 3.1 mL in the thoracic spine and 3.8 mL in the lumbar spine.

Table 2.   Clinical characteristics of the registered patients

Item	Value
Gender, male/female (percentage)	123/362 (25.4/74.6%)
Age (years), mean ± SD (range)	81.4 ± 8.0 (46–100)
Weight (kg), mean ± SD (range)	49.5 ± 11.4 (21–109)
Height (cm), mean ± SD (range)	152.1 ± 8.8 (130–178)
No. of patients with a history of vertebral fracture (percentage)	243 (50.1%)
No. of fractured vertebrae per patient, mean ± SD (range)	1.4 ± 0.8 (1–7)

SD: standard deviation
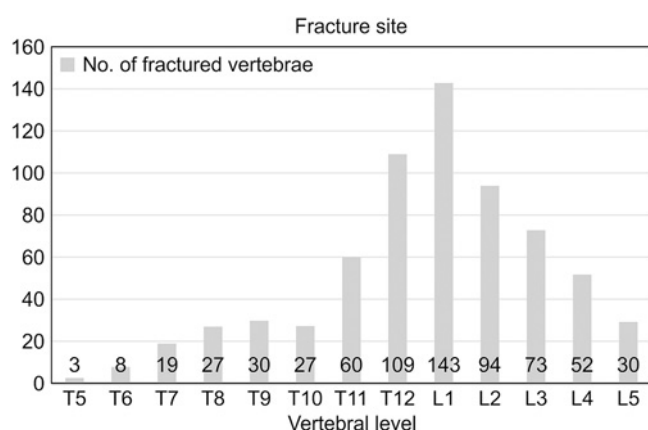
Figure 1.   The cumulative number of pre-procedural fractures by fracture site

Safety evaluation

None of the patients undergoing PVP at the four institutions had adverse events and health hazards causally related to PVP, including hazardous extra-vertebral cement leakage. Seven patients had other adverse events without requiring intensive treatment, including five with a transient decrease in blood pressure during treatment (CTCAE Grade 2), which was considered to be a vagal reflex; one with a transient oxygen desaturation (CTCAE Grade 2), which was considered a sedative overdose, and one with a transient fever (CTCAE Grade 1), which was considered to be a postoperative reactive change. During the follow-up period, a total of six patients died, including three dying of their primary disease (lung cancer), one patient each with liver cirrhosis and hepatoma, cerebral hemorrhage, and aortic dissection, with none of these deaths judged to have any causal relationship with PVP.

Table 4 shows the occurrence of extra-vertebral cement leakage associated with PVP. As noted earlier, all leakages detected by imaging were asymptomatic, without any direct health hazard. Therefore, the safety of PVP was judged to be equivalent to that of BKP, given that no serious cement leakage-associated adverse events requiring intensive treatment occurred in the 485 patients available for safety evaluation. In addition, cement leakage occurred in 35.7% of the patients undergoing PVP (between 26.2% and 38.4%), a rate similar to that in patients undergoing BKP. **Table 5** shows the incidence of new vertebral compression fractures during a one-year follow-up period. Post-treatment investigations, including telephone follow-up, showed that new fractures of adjacent vertebral bodies occurred in 6.6% of the 361 patients undergoing PVP, while fractures of distant vertebral bodies occurred in 12.7% of these patients (**Table 5**). New vertebral compression fractures occurred in 18.6% (between 8.9% and 20.7%) of the patients undergoing PVP, again at a similar rate to those undergoing BKP.

Efficacy evaluation

Table 6 shows the pain relief based on changes in pain score at rest and with activity before PVP, at discharge after PVP, and at one-year follow-up after PVP. The pain scores improved from before to after PVP both at rest ($P < 0.01$) and with activity ($P < 0.01$). Comparing the reduction rates, the pain scores reduced more during activity than at rest. Pain relief was maintained over a one-year follow-up period. The pain score at rest one-year after PVP was not different from that at discharge after PVP, but the pain score with activity one year after PVP was lower than that at discharge after PVP ($P < 0.01$).

While a total of 206 patients (42.5%) had difficulty walking before PVP, only 50 (10.3%) had difficulty walking after PVP, and the number of patients capable of walking independently significantly increased to 436 (89.7%) at discharge ($P < 0.01$).

Four of 19 patients had good pain control, leading to opioid discontinuation after PVP, but this improvement failed to achieve statistical significance due to the small sample size. None of the patients had increased or newly required opioids after PVP.

Discussion

PVP was more likely considered to be associated with frequent extra-vertebral bone cement leakage causing health damage than BKP, given its low bone cement viscosity and cement injection without creating a cavity. To address this

Table 3. Patient information at the time of first visit

Item	Value
No. of patients with primary disease, osteoporosis/unknown (percentage)	483/2 (99.6/0.4%)
Mean time (days) from injury to hospital visit (range)	69.7 (0–1487)
Mean pain score at hospital visit, at rest/with activity	2.7/7.2
Difficulty in walking at hospital visit (percentage)	206 (42.5%)
Presence of bone-marrow edema on MRI (percentage)	441 (90.9%)
No. of patients undergoing diagnostic imaging modality prior to surgery, MRI/CT/bone scintigram (percentage)	470/15/1 (96.9/3.1/0.2%)

MRI: magnetic resonance imaging

CT: computed tomography

Table 4. Incidence of cement leakages associated with percutaneous vertebroplasty

Item	Total	Leakage site (multiple entries allowed)		
		Intervertebral disc	Spinal canal	Blood vessel
No. of patients with cement leakage associated with PVP (percentage)	173 (35.7%)	68 (14.0%)	26 (5.3%)	93 (19.2%)

PVP: percutaneous vertebroplasty

Table 5. Incidence of new vertebral compression fractures in 361 patients

Item	Total	Fracture site (multiple entries allowed)	
		Adjacent vertebrae	Distant vertebrae
No. of patients with new vertebral compression fractures after PVP (percentage)	67 (18.6%)	24 (6.6%)	46 (12.7%)

PVP: percutaneous vertebroplasty

Table 6. Pain score before and after percutaneous vertebroplasty

Item	Value
At hospital visit before PVP, at rest/with activity	2.7/7.2
At discharge after PVP, at rest/with activity	0.6/2.2
At one-year follow-up after PVP, at rest/with activity	0.5/1.6

PVP: percutaneous vertebroplasty

debate, we retrospectively examined the safety and efficacy of PVP-treated patients over one year from April 2017 to March 2018.

The safety of PVP was equivalent to that of BKP with no serious cement leakage-associated adverse events requiring treatment reported in the 485 patients available for safety evaluation, thus meeting the success criterion for this study (see Appendix 1). All leakages were found by imaging, were asymptomatic, and associated with no direct health hazards. Therefore, it is suggested that PVP has no major safety problems.

Of all extra-vertebral cement leakages associated with PVP, 27% and 72% are reported to be present on radiographs and CT, respectively, while causing no symptoms [18]. Chen et al. also found that 52% of patients undergoing PVP had cement leakages in a range of sites, including the intervertebral space (22%), puncture pathway (19%), perivertebral body (25%), vertebral vein (33%), and pulmonary vein (2.9%); however, all these patients were asymptomatic[19]. In our study, of all patients undergoing PVP, 173 (35.7%) had extracorporeal cement leakages while being asymptomatic, a rate similar to that reported in literature and equivalent to that in those undergoing BKP.

Serious complications have been reported to occur in conjunction with PVP at a frequency of approximately 1.5% (7/ 455), and these include asthma, asymptomatic pulmonary embolism, hematoma, urinary tract infection, thecal sac injury, osteomyelitis, and epidural cement leakage requiring decompression [20]. In our study, adverse events other than these were reported in seven patients, including a transient decrease in blood pressure, which was considered to be a vagal reflex (n = 5), transient oxygen desaturation, which was considered to be a sedative overdose (n = 1), and transient fever, which was considered to be a postoperative reactive change (n = 1), all of which resolved with no subsequent complications.

While the patients undergoing PVP had a mean age of over 80 years in this study, none were treated under general anesthesia and had no anesthesia-associated adverse events. Given that PVP may also be effectively implemented in patients over 90 years [21], PVP may represent a preferred treatment option in Japan as an increasingly aging society.

Notably, the frequency of adjacent vertebral fractures is not only different between PVP and conservative treatment in a meta-analysis of 10 RCTs [22], but also between PVP and BKP [23]. It has been reported that the incidence of new painful fractures is not significantly different between PVP and conservative treatment (14% and 12%, respectively) or the incidence of new fractures detected on imaging (19.3% and 23.6%, respectively) [24]. Wardlaw et al. reported that 21 (14%) participants undergoing BKP had new clinical vertebral fractures [17]. In our series, investigations, including telephone follow-up, were conducted in a total of 361 patients undergoing PVP and demonstrated that 67 of these patients (18.6%) had new secondary fractures, a rate similar to that of patients undergoing BKP.

Concerning the efficacy endpoints evaluated, the pain score improved from before to after PVP, suggesting a significant role for PVP in alleviating pain. Furthermore, of the 206 patients who had difficulty walking before PVP, 156 (75.7%) resumed walking at discharge in this study. Although pain evaluation remains a challenge, as patients' self-rating of pain often changes with psychological factors and different environments [25], the improvement in ambulatory ability seen in this study appears to be a respectable outcome reflecting the objective effectiveness of PVP.

There were some limitations to this study. First, its retrospective nature and the loss of 124 of 485 patients (25.6%) at one-year follow-up may have led to an overestimation of the treatment effect. The study data were derived from only four tertiary care centers and may not represent those associated with current PVP practices in Japan. Nonetheless, the study data may serve as a benchmark for future PVP practices throughout Japan. While the clinical course of patients undergoing PVP remained asymptomatic during the one-year follow-up, the clinical course beyond post PVP one-year post-PVP remains unknown and may evolve and become symptomatic over the longer term. The details of the surgical procedure may vary depending on the operator and the institutional principles. Further research is required to investigate if there are any adverse effects unique to Japanese patients undergoing PVP and, if any, to identify them to provide precautions for PVP in clinical practice in Japan, while the safety and efficacy of PVP have been established worldwide.

Conclusion

PVP is considered a safe and effective option. Furthermore, it appears to be an excellent treatment modality, given its favorable risk profile, including the risk of extra-vertebral bone cement leakage, which has been shown to lead to no health hazards in this study.

Appendix 1

Rationale for determining the sample size required for the safety evaluation of PVP

Cement leakage is a major issue with PVP and balloon kyphoplasty (BKP) as a potential cause of severe adverse events associated with spinal cord compression. Therefore, the study planned the number of patients required to confirm the incidence of cement leakage and associated adverse events in patients undergoing PVP, based on data from the BKP study conducted by Wardlaw et al. [17], which demonstrated that while no cement leakage-associated adverse events required treatment, cement leakage occurred in 48 of 149 patients (32.2%). This led to the true incidence of severe adverse events being estimated as 2.01%, in light of the one-sided 95% confidence interval for the binomial distribution. Thus, the minimum number of patients required for

this hypothesis testing was set to 250, and the dropout rate was set to 5%. If a total of 237 patients were available for safety evaluation in this study and if no severe adverse events were observed, the maximum true adverse event incidence would be 1.26% with a probability of 5% or less, which was lower than that observed with BKP. Even when one serious adverse event was observed, the maximum true adverse event incidence was 1.99% with a probability of 5% or less, which was lower than that observed with BKP.

Conflict of interest: The authors declare that they have no conflicts of interest to report. A summary of this study has been presented at JSIR, August 25-27th, 2020, Kobe, Japan.

Abbreviations: ADL: activities of daily living. BKP: balloon kyphoplasty. CT: computed tomography. CTCAE: Common Terminology Criteria for Adverse Events. PVP: percutaneous vertebroplasty. QOL: quality of life. RCT: randomized control trial. SD: standard deviation.

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