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ORIGINAL RESEARCH

# Percutaneous Vertebroplasty Is Not a Risk Factor for New Osteoporotic Compression Fractures: Results from VERTOS II

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**BACKGROUND AND PURPOSE:** PV is increasingly used as treatment for osteoporotic VCFs. However, controversy exists as to whether PV increases the risk for new VCFs during follow-up. The purpose of our research was to assess the incidence of new VCFs in patients with acute VCFs randomized to PV and conservative therapy.

**MATERIALS AND METHODS:** VERTOS II is a prospective multicenter randomized controlled trial comparing PV with conservative therapy in 202 patients. Incidence, distribution, and timing of new VCFs during follow-up were assessed from spine radiographs. In addition, further height loss during follow-up of treated VCFs was measured.

**RESULTS:** After a mean follow-up of 11.4 months (median, 12.0; range, 1–24 months), 18 new VCFs occurred in 15 of 91 patients after PV and 30 new VCFs in 21 of 85 patients after conservative therapy. This difference was not significant ($P = .44$). There was no higher fracture risk for adjacent-versus-distant vertebrae. Mean time to new VCF was 16.2 months after PV and 17.8 months after conservative treatment (logrank, $P = .45$). The baseline number of VCFs was the only risk factor for occurrence (OR, 1.43; 95% CI, 1.05–1.95) and number ($P = .01$) of new VCFs. After conservative therapy, further height loss of treated vertebrae occurred more frequently (35 of 85 versus 11 of 91 patients, $P < .001$) and was more severe ($P < .001$) than after PV.

**CONCLUSIONS:** Incidence of new VCFs was not different after PV compared with conservative therapy after a mean of 11.4 months' follow-up. The only risk factor for new VCFs was the number of VCFs at baseline. PV contributed to preservation of stature by decreasing both the incidence and severity of further height loss in treated vertebrae.

**ABBREVIATIONS:** CI = confidence interval; FREE = Efficacy and Safety of Balloon Kyphoplasty Compared with Nonsurgical Care for Vertebral Compression Fracture; OR = odds ratio; PV = percutaneous vertebroplasty; VAS = Visual Analogue Scale; VCF = vertebral compression fracture; VERTOS = Percutaneous Vertebroplasty Versus Conservative Therapy



VCFs are the most common fractures associated with osteoporosis.[1] In the elderly population with osteoporosis, VCFs may lead to morbidity and even mortality due to incapacitating back pain, decreased daily activity, and increased days of bed rest.[2,3] In addition, deterioration of stature, such as severe thoracic kyphosis, may contribute to morbidity by decreased pulmonary function or higher risk of falling. Fortunately, only a minority of VCFs cause such severe pain that patients seek medical attention.[4] When pain response to analgesics is insufficient during several weeks, PV is increasingly used as a minimally invasive technique to induce durable pain relief. However, some authors believe that PV is associated with a higher incidence of new VCFs as a result of the augmented stiffness of the treated vertebra, related to the amount of injected cement or by cement leakage in the adjacent vertebral disk space.[5-8] Others dispute this assumption and consider the incidence of new VCFs dependent on the presence and severity of osteoporosis.[9-13] To elucidate this controversy, we assessed the incidence of new VCFs during follow-up in 202 patients with acute VCFs randomized to PV and conservative therapy from VERTOS II.[14] In addition, we assessed further height loss of the treated vertebrae with both therapies.

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## Materials and Methods

### *Patients*

The detailed study design has previously been published.[14] In short, we performed a randomized controlled trial comparing PV with conservative therapy in selected patients with acute VCF in 5 large teaching hospitals in the Netherlands and 1 in Belgium. Inclusion criteria were the following: 1) VCF on spine radiograph (minimal 15% loss of height), 2) level of VCF T5 or lower, 3) back pain for ≤6 weeks, 4) VAS score of ≥5 on a 0–10 scale, 5) bone edema of the fractured

**Table 1: Baseline characteristics of 202 randomized patients**

| | PV | Conservative Therapy | *P* Value |
|---|---|---|---|
| No. of patients | 101 | 101 | |
| Age | 75.2 ± 9.8 | 75.4 ± 8.4 | .90 |
| Female sex | 70 (69%) | 70 (69%) | 1.0 |
| Duration of back pain (days) | 29.3 ± 17.1 | 26.8 ± 16.0 | .46 |
| Initial VAS | 7.8 ± 1.5 | 7.5 ± 1.6 | .12 |
| Mean no. of VCFs at baseline (range) | 2.4 ± 1.9 (1–5) | 2.1 ± 1.5 (1–5) | .24 |
| No./grading of VCFs with bone edema | 136 | 120 | |
| Mild | 57 | 55 | .59 |
| Moderate | 58 | 45 | |
| Severe | 21 | 20 | |
| Wedge | 90 | 97 | .18 |
| Biconcave | 46 | 23 | |
| Crush | 0 | 0 | |
| Vertebral level with bone edema | | | |
| T5-T10 | 19 | 32 | .16 |
| T11-L2 | 91 | 66 | |
| L3-L5 | 29 | 28 | |
| Bone density (*t*-score) | −3.0 ± 1.17 | −3.0 ± 1.05 | .78 |

vertebral body on MR imaging, 6) focal tenderness on the VCF level, and 7) decreased bone attenuation with *t*-scores equal or less than −1. Exclusion criteria were the following: 1) severe cardiopulmonary comorbidity, 2) untreatable coagulopathy, 3) infection, 4) suspected alternative underlying malignancy, 5) radicular syndrome, 6) myelum compression syndrome, and 7) contraindication for MR imaging. The study protocol was approved by the institutional review board at each participating center.

### *Procedures*

Participants were randomly assigned to PV or conservative therapy. PV was performed under biplane fluoroscopy with bilateral transpedicular injection of bone cement. Native CT of the spine was performed to detect possible cement leakage. Conservative therapy consisted of analgesics optimized in classification and dose by an internist on a daily basis. Patients in both treatment groups received bisphosphonates, calcium supplementation, and vitamin D. Symptomatic new VCFs were treated according to the originally allocated treatment strategy.

### *Imaging*

At baseline, radiography and MR imaging of the spine were performed. Spine radiographs were repeated at 1-, 3-, and 12-month follow-up. Two radiologists independently performed semiquantitative and quantitative morphometric assessments at baseline and follow-up imaging.[15,16] A "new VCF" was defined as a decrease of at least 4 mm in vertical dimension.[17] Height loss in new VCFs was categorized as mild, moderate, and severe. Distribution of new VCFs was classified as adjacent to a treated level, between treated levels, and distant to a treated level.[18] "Further height loss" during follow-up of treated baseline VCFs with bone edema was defined as height loss of ≥4 mm and was categorized as moderate (4–7 mm) and severe (>8 mm). Disagreement between observers was resolved in a consensus meeting. Because bone cement is radiopaque, treatment assignment could not be blinded.

### *Statistical Analysis*

Patient characteristics were compared. A *t*-test was used for means, and a $\chi^2$ test for proportions. The incidence and timing of new VCFs were analyzed by using survival analysis. The cumulative incidence was calculated by using Kaplan-Meier estimates. Logistic regression analysis was used to assess a possible relation between the incidence of new VCFs and the following factors: age, sex, randomization, baseline VAS-score, bone mineral attenuation, number of prevalent fractures, fracture severity, number of vertebral levels treated, mean amount of bone cement injected per vertebra, cement leakage into the disk, cement leakage into the soft tissue around the vertebra, and cement leakage into the veins. Linear regression analysis was used to determine risk factors for the number of new VCFs. Analysis was by intention to treat.

Statistical analysis was performed with the Statistical Package for the Social Sciences, Version 15.0.1 (SPSS, Chicago, Illinois). The VERTOS II study is registered with ClinicalTrials.gov, with the number NCT00232466.

## Results

Of 934 patients who were screened between October 2005 and June 2008, 202 met the inclusion criteria and agreed to participate in the study. Of the 202 participating patients, 101 were assigned to PV and 101 to conservative therapy. Baseline characteristics were similar (Table 1). Informed consent was withdrawn after randomization by 6 patients assigned to conservative therapy and 2 patients assigned to PV. These patients had no therapy, and follow-up could not be obtained. Six patients assigned to PV did not receive this treatment because of poor health ($n = 3$) and spontaneous pain relief ($n = 3$). Follow-up was obtained in 5 of these 6 patients. Ten patients assigned to conservative therapy with ongoing invalidating pain requested and received PV during follow-up. Five of these 10 patients withdrew informed consent, so the PV procedure could not be documented and analyzed. Finally, 81% of the participants completed the follow-up at 1 year.

PV was performed in 98 patients on 134 vertebrae in 103 procedures. The mean volume of injected cement per vertebral body was 4.10 mL (range, 1–9 mL). CT of the 134 treated vertebral bodies showed cement leakage in 97 (72%). Most leakages were into adjacent disks or segmental veins; there was

**Table 2: Distribution of new VCFs**

| Distribution | PV ($n = 91$) | Conservative Therapy ($n = 85$) | $P$ Value |
|---|---|---|---|
| Adjacent | 7 | 11 | .23 |
| Between | 4 | 3 | |
| Distant | 7 | 16 | |

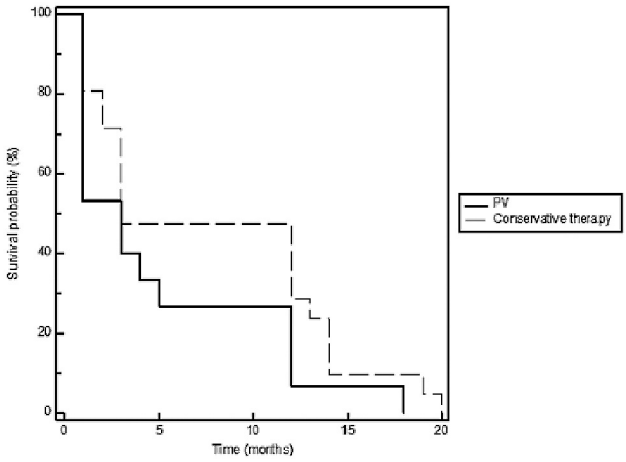


**Fig 1.** Kaplan-Meier survival curve for the timing of new VCFs after PV and conservative therapy.

no leakage into the spinal canal. All patients remained asymptomatic.

### *New VCFs during Follow-Up*

After a mean follow-up of 11.4 months (median, 12.0; range, 1–24 months), 18 new fractures were observed in 15 of 91 patients treated with PV and 30 new vertebral fractures were apparent in 21 of 85 patients treated with conservative therapy. This difference in incidence was not significant ($P = .44$). New VCFs occurred at 4.6 ± 5.4 months after PV and 6.1 ± 5.9 months after conservative therapy ($P = .48$).

The distribution of new VCFs is shown in Table 3. Distribution of location was not significantly different ($P = .23$). There was no higher fracture risk for adjacent-versus-distant vertebrae.

Time to new VCF is graphically displayed in Fig 1. The Kaplan-Meier estimate of the mean time to incident was 16.2 months after PV and 17.8 months after conservative treatment. This difference was not significant (logrank, $P = .45$).

The baseline number of vertebral fractures was the only risk factor for the occurrence of new VCFs (OR, 1.43; 95% CI, 1.05–1.95) and also for the number of new VCFs ($P = .01$).

Further height loss during follow-up of treated baseline VCFs with bone edema was observed in 11 vertebrae in 11 of 91 patients after PV and in 39 vertebrae in 35 of 85 patients after conservative therapy. Further height loss occurred more frequently in patients after conservative therapy (35 of 85 versus 11 of 91 patients, $P < .001$). Severity grading of further height loss is shown in Table 3. After conservative therapy, further height loss was significantly more severe than after PV ($P < .001$)

**Table 3: Height loss of the treated VCFs between baseline and last follow-up**

| Further Height Loss of Treated Vertebrae | PV ($n = 136$ vertebrae) | Conservative Therapy ($n = 120$ vertebrae) | $P$ Value |
|---|---|---|---|
| None (0–3 mm) | 118 | 74 | <.001 |
| Moderate (4–7 mm) | 7 | 28 | |
| Severe (≥8 mm) | 4 | 11 | |

## Discussion

We found that PV does not increase the risk of new vertebral fractures in the first year. The incidence and distribution of new VCFs were similar after PV and conservative therapy. After PV, there was no higher fracture risk for adjacent-versus-distant vertebrae. After both PV and conservative therapy, the only risk factor for the occurrence of new VCFs was the number of VCFs at baseline. This number of baseline VCFs in turn is associated with the severity of osteoporosis. Thus, the occurrence of new VCFs is due to the ongoing osteoporosis only and not to the type of therapy.

Our study shows that PV prevented further height loss of the treated fractured vertebral bodies in most patients. Apparently, the injected cement strengthened the fractured vertebral body. This is an important advantage in the prevention of morbidity associated with deterioration of stature such as severe kyphosis with decreased pulmonary function. PV not only decreased the incidence but also the severity of further height loss in affected vertebrae, thus further contributing to preservation of stature.

Our study is the first randomized controlled trial evaluating the risk of new VCFs in the first year after PV in a large patient cohort. The only limitation of our study was the inability to blind treatment assignment due to the radio-opacity of the bone cement used in PV. A study with a comparable design is the FREE study, which compared kyphoplasty with conservative treatment in 300 patients with acute VCFs.[19] Kyphoplasty involves an inflatable bone tamp to preform a space for the bone cement instead of a direct cement injection into the vertebral body as in PV. In this FREE study, an equal incidence of new VCFs was also found after kyphoplasty and conservative treatment but risk factors for new VCFs, distribution of new VCFs, and further height loss of treated VCFs at baseline were not analyzed.

The findings of our study and the FREE study are in concordance with other studies.[9-13,20] On the other hand, some studies have reported an increased risk of new VCFs after PV.[5,6,8,20,21] However, most of these studies were small nonrandomized follow-up only studies, lacking a control group without intervention.

Some noncontrolled follow-up studies after PV reported that new VCFs, more often located adjacent to the vertebroplasty level, allegedly contributed to the increased dimensional stability of the cemented vertebral body.[6,8,22,23] However, in our randomized study, no difference in location distribution of new VCFs was found after PV and conservative therapy. In addition, after PV, the risk for a new VCF adjacent to the cemented level was equal to the risk of a new VCF at a distant level.

In our study, cement leakage after PV outside the vertebral body was frequently detected with CT. Most leakages were into adjacent disks or segmental veins; none were into the spinal canal. All patients remained asymptomatic. Cement leakage was not associated with the occurrence of new VCFs during follow-up, in contradiction to some other studies in which leakage into an adjacent disk was considered a risk factor for new VCFs.[5,24] Postprocedural CT is not needed in routine daily practice; it is only needed in cases with clinical symptoms or significant volumes of cement leakage.

## Conclusions

The incidence of new VCFs in patients with an acute osteoporotic VCF was not different after PV compared with conservative therapy in the first year of follow-up. The only risk factor for the occurrence of new VCFs was the number of VCFs at baseline. PV contributed to preservation of stature by decreasing the incidence and severity of further height loss in treated vertebrae.

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