Cardiovasc Intervent Radiol (2019) 42:991–1000
https://doi.org/10.1007/s00270-019-02205-w

CLINICAL INVESTIGATION NON-VASCULAR INTERVENTIONS

Percutaneous Vertebroplasty is no Risk Factor for New Vertebral Fractures and Protects Against Further Height Loss (VERTOS IV)

Cristina E. Firanescu[1] · Jolanda de Vries[1,2] · Paul Lodder[2] · Marinus C. Schoemaker[1] · Albert J. Smeets[1] · Esther Donga[1] · Job R. Juttmann[1] · Caroline A. H. Klazen[3] · Otto E. H. Elgersma[4] · Frits H. Jansen[5] · Irene van der Horst[5] · Marion Blonk[5] · Alexander Venmans[1] · Paul N. M. Lohle[1]

Received: 13 November 2018 / Accepted: 11 March 2019 / Published online: 2 April 2019

Abstract

Background Percutaneous vertebroplasty (PV) is an alternative option to treat pain after an osteoporotic vertebral compression fracture (OVCF). Controversy exists as to whether PV increases the risk of new OVCFs or prevents further vertebral height loss in treated levels. We assessed both during 1-year follow-up in patients with acute OVCF randomised to PV or a sham procedure.

Methods VERTOS IV is a prospective, multicentre, randomised controlled trial comparing PV with sham therapy in 180 patients. New OVCFs and further vertebral height loss were assessed at 3, 6, and 12 months.

Results After a median follow-up of 12 months (interquartile range (IQR) = 12–12) 31 new fractures were reported in 15 patients from the PV group and 28 new fractures in 19 patients from the sham group. The occurrence of new vertebral fractures did not significantly differ between the groups ($\chi^2(1) = 0.83$, $p = 0.36$, OR = .71, 95%CI = 0.33–1.50). There was no higher fracture risk of adjacent versus distant vertebrae. After sham procedure, further height loss of treated vertebrae occurred more frequently (7 patients (8%) in the PV group and 39 (45%) in the sham group ($\chi^2(1) = 28.85$, $p < 0.001$, OR = 9.84, 95%CI = 4.08–23.73)) and was more severe ($p < .001$) than after PV.

Conclusions The risk of further vertebral height loss is significantly lower after PV compared to a sham intervention, i.e. PV protects against progressive vertebral height loss. In addition, PV does not increase the risk of new adjacent and distant OVCFs.

Level of Evidence Level 1a, therapeutic study.
ClinicalTrials.gov number, NCT01200277

Keywords Osteoporotic percutaneous vertebroplasty (PV) · Vertebral compression fracture (OVCF) · Visual analogue scale (VAS) · Polymethylmethacrylate (PMMA) · VERTOS IV · Randomised controlled trial (RCT)

Introduction

A clinically diagnosed thoracic or lumbar osteoporotic vertebral compression fracture (OVCF) in the elderly can be regarded as a risk factor for subsequent long-term morbidity, especially in women, and for mortality in both genders [1, 2]. In most patients with an acute OVCF,

Cristina E. Firanescu, Alexander Venmans, and Paul N. M. Lohle have contributed equally to this work.

✉ Cristina E. Firanescu
crisfiranescu@hotmail.com

[1] Departments of Radiology and Internal Medicine, Elisabeth TweeSteden Hospital, Hilvarenbeekseweg 60, 5022 GC Tilburg, The Netherlands

[2] Department of Medical and Clinical Psychology, Tilburg University, Warandelaan 2, 5037 AB Tilburg, The Netherlands

[3] Department of Radiology, Medisch Spectrum Twente, Koningsplein 1, 7512 KZ Enschede, The Netherlands

[4] Department of Radiology, Albert Schweitzer Hospital, Albert Schweitzerplaats 25, 3318 AT Dordrecht, The Netherlands

[5] Department of Radiology, Catharina Hospital, Michelangelolaan 2, 5623 EJ Eindhoven, The Netherlands

pain decreases significantly with conservative therapy, predominantly in the first 6 months [3]. When pain response to analgesics is insufficient, percutaneous vertebroplasty (PV) is considered an option. PV is a minimally invasive procedure involving injection of polymethylmethacrylate (PMMA) into a fractured vertebral body and can be used as an analgesic. Side effects and complications of PV were reported by some authors who believed that PV is associated with a higher incidence of new OVCFs as a result of cement leakage in the adjacent vertebral disc space or due to augmented stiffness of the treated vertebral body, related to the amount of injected cement [4–8]. Others disputed this assumption and considered the incidence of new OVCFs dependent on the presence and severity of osteoporosis or related to the number of fractures at baseline [9–12]. Patients with osteoporosis and one or more OVCFs at baseline have a fivefold (cumulative incidence of 6.6%) increased risk of a new OVCF during 1-year follow-up [13]. Whether the injection of PMMA increases the risk during 1 year after treatment compared to a sham intervention is still under debate.

Decreased incidence of further height loss in treated vertebral bodies after PV was earlier described in a randomised trial that compared PV with conservative therapy [12].

The VERTOS IV study is a prospective, multicentre, randomised controlled trial (RCT) assessing pain relief after PV compared to sham during 1-year follow-up. In this article we describe in more detail the incidence of new OVCFs and further vertebral height loss in patients randomised to PV or sham intervention from VERTOS IV.

Methods

Study Design and Patients

This sham RCT was carried out by four large teaching community hospitals in the Netherlands. The inclusion criteria were as follows: age of 50 years or older; 1–3 OVCFs from level T5 down to L5, focal back pain at the fracture(s) level(s) for 6 weeks or less, a visual analogue scale (VAS) score of 5 or higher, and a decreased bone density (T score ≤ -1). With imaging, a minimum of 15% vertebral height loss was required as well as vertebral body bone oedema on MRI. Independent confirmation of the patient's focal back pain relating to the OVCF was provided by an internal medicine specialist performing physical examination prior to randomisation. Exclusion criteria were as follows: severe cardiopulmonary morbidity, untreatable coagulopathy, systemic or local spine infection, suspected malignancy, neurologic symptoms, and inability to obtain MRI. MRI was required for participation in this study, and as a result, patients with contraindication for MRI were excluded.

The institutional review board at each participating centre approved the study protocol. Patients provided written informed consent. More detailed information of this trial, including the protocol, patient selection, and clinical outcome measures, is described in detail elsewhere [14].

Procedures

Prophylactic PV was not performed in asymptomatic patients. Patients were randomly allocated to PV or the sham intervention using computer randomisation codes with a block size of six with a maximum sample size of 84 for each participating centre (randomisation ratio 1:1). Masking was applied for the participating patients, internal medicine specialist, and outcome assessors. The assignment stayed concealed for all patients and study personnel involved in the post-interventional care during the one-year follow-up. Masking was not possible for the interventional radiologists during the procedure and for the two radiologists who assessed the imaging during follow-up.

All patients received local subcutaneous infiltration with 1% lidocaine followed by periosteal 0.25% bupivacaine at each pedicle. In every sham and cement case, two stab incisions were made at the level of the vertebral body in question. Next, the sealed randomisation envelope was opened and the content was communicated to the interventional radiologists. In both groups, bone biopsy needles were placed bilaterally: standard transpedicular placements for PV or just against the periosteum for sham. Cement was prepared in both groups with an activated cement mixer in the interventional radiology suite in the immediate proximity of the patient. As a result, the mixing sound could be heard and the PMMA (Vertaplex®, Stryker, Kalamazoo, USA) was smelled by everyone in the room, including the patient. In the PV group, a cement injector was attached to the needles that had previously been placed. In the sham group we simulated the injection phase of the procedure; verbal and physical cues were performed to simulate PV. PMMA was infused using standard techniques in the PV group. The infusion in the PV group was stopped when a proper maximum filling of the total vertebral body was obtained in AP and sagittal projection or when cement leakage or migration was noticed into the intervertebral disc space, epidural, or paravertebral veins. In patients with multiple fractures, all OVCFs were treated contemporaneously according to the assigned group. Additional analgesics were allowed for patient comfort during the procedure. All PV patients underwent a post-procedural CT scan, whereas sham patients received a scout only. The threshold for describing leakage was anything perceptible on CT.

The patients (all outpatient procedures) were ambulant and treated with a maximum hospital stay of 12 h after the intervention. Because both patients and nurses at the ward were blinded to the intervention, all patients received the same patient care during hospital stay and at discharge. At discharge, all patients were advised to mobilise. There were no other medical aids recommended (e.g. physiotherapy, corset). The osteoporotic medication was prescribed following the standard protocol used in all patients at the participating institutions with fractures due to osteoporosis. Hence, both groups received the same medications during follow-up: calcium/vitamin D and bisphosphonates. Pain medication was prescribed or continued if necessary.

Imaging Measurements

All imaging from the participating hospitals was reviewed by two independent diagnostic radiologists at the coordinating centre. They independently performed semi-quantitative and quantitative morphometric assessments at baseline and follow-up imaging [15, 16].

At baseline, both AP and sagittal thoracic and lumbar plain X-rays and whole-spine MR imaging were performed. An OVCF was defined when more than 15% vertebral height loss occurred. Bone oedema was identified on the sagittal STIR MRI sequence. Osteonecrosis was defined as intravertebral body vacuum cleft with collection of fluid (hyperintense signal on T2-weighted images), air (signal void on all images), or both [17]. The CT scans were reviewed in the PV group. The threshold for describing cement leakage was anything perceptible on a CT axial slice.

Thoracic and lumbar (AP and sagittal) X-rays were obtained at 3-, 6-, and 12-month follow-up, and MRI was performed in case of secondary symptomatic OVCFs. A new OVCF was defined as a decrease of at least 4 mm in vertical dimension [18]. Height loss in a new OVCF was categorised as mild, moderate, and severe. No magnification was used. Distribution of new OVCFs was classified as adjacent to the treated level, between treated levels, and distant to the treated level [19]. A new OVCF in relation to osteonecrosis at baseline was documented. Further height loss during follow-up of treated baseline OVCFs with bone oedema was defined as height loss of 4 mm or more, categorised as moderate (4–7 mm) and severe (> 8 mm). Disagreement between the observers was resolved in a consensus meeting. Leakage of cement was recorded even for very small cement traces outside the target vertebra and defined as type 1 (disc above), type 2 (disc below), type 3 (perivertebral soft tissue), type 4 (perivertebral veins), type 5 (pulmonary), and type 6 (spinal canal). Because bone cement is radio-opaque, treatment assignment could not be blinded during assessment.

Statistical Analysis

Means and standard deviations were reported for normally distributed continuous variables. In case of non-normality, we reported the median and interquartile range (IQR). Independent samples t-tests were used to compare mean differences between groups, and Chi-square tests were used to assess differences in proportions. Associations between ordinal variables were assessed using Spearman's rho. The incidence and timing of new OVCFs was analysed using survival analysis. The cumulative incidence was calculated using Kaplan–Meier estimates. Differences between survival curves were investigated using the log-rank test. We assessed a possible relation between the incidence of new OVCFs and the following factors: age, gender, randomisation, baseline VAS score, bone mineral density, fracture level, number of prevalent fractures, fracture severity, presence of osteonecrosis, number of vertebral levels treated, mean amount of bone cement injected per vertebra, cement leakage into the disc, 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 OVCFs and progressive height loss. Lastly, we used mixed modelling in SPSS to conduct a repeated-measures multilevel analysis (level 1 = time point; level 2 = individual) to assess predictors of the change in VAS scores over time. The repeated measures were modelled according to the first-order autoregressive (AR1) error structure. *P*-values smaller than 0.05 were considered to indicate statistical significance.

Results

Between April 2011 and April 2014, 1280 patients with local back pain and one to three OVCFs, aged 50 years or older, were screened for eligibility, of whom 180 were randomly allocated to treatment. (Ninety-one patients received PV, and 89 patients received a sham procedure.) One hundred fifty-six patients who would have been eligible for randomisation declined to participate for different reasons including patients' demand for open-label PV. After randomisation a total of four patients were excluded. One patient was excluded from the PV group, because of the presence of more than three fractured levels. Two patients were excluded from the sham group because multiple myeloma was diagnosed after randomisation. One patient was excluded because of a missing intake form. Thirteen patients died of unrelated causes during 1-year

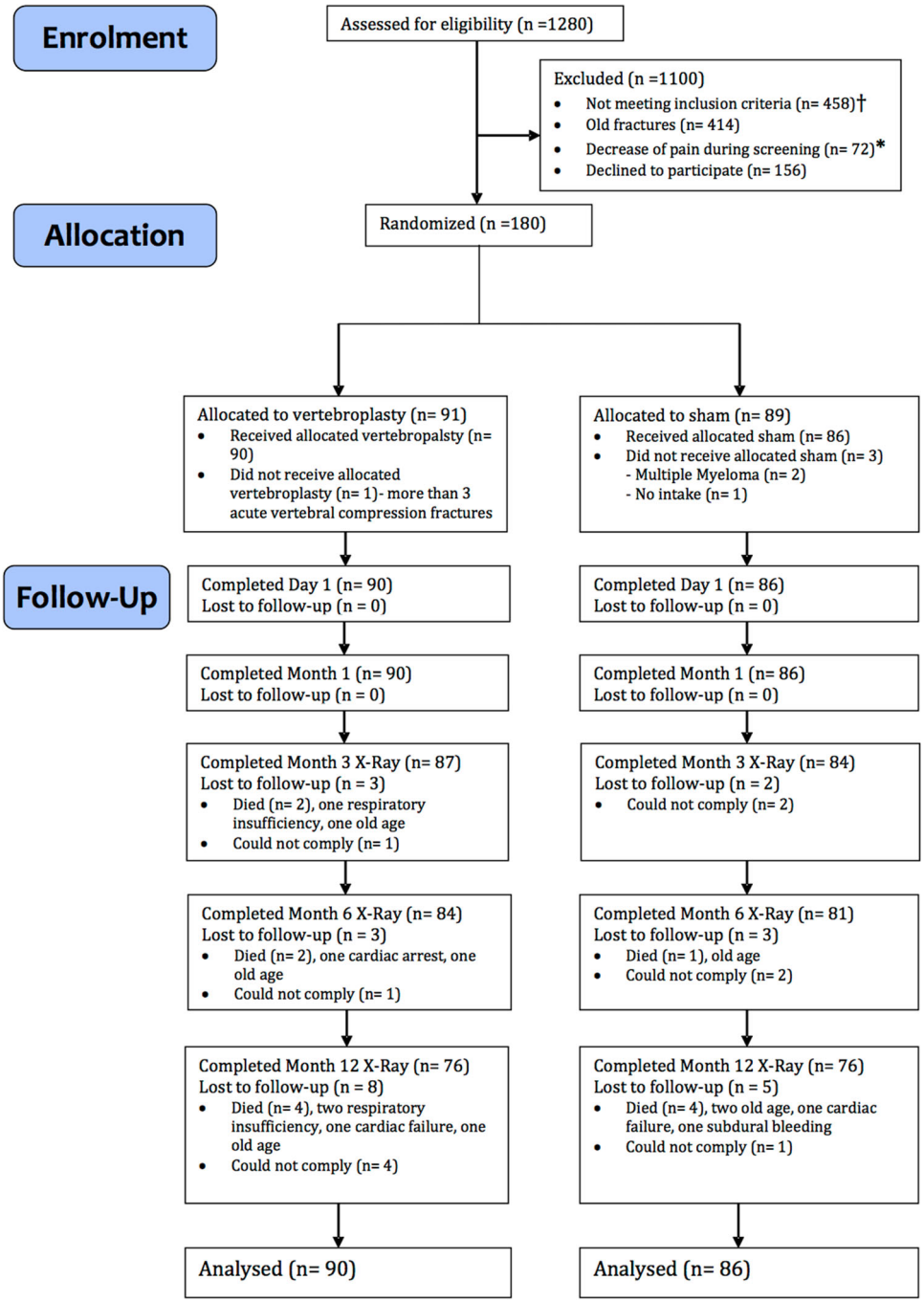

Fig. 1 Enrolment and outcomes. PV = percutaneous vertebroplasty. § Pain > 6 weeks, older fracture diagnosed on previous X-ray, no bone oedema. * VAS lower than 5 while waiting for treatment, and thus no longer met inclusion criteria for randomisation. Patients who missed an interim assessment by not returning the questionnaire, holiday, or hospitalisation for an unrelated reason to the study were included in subsequent assessments

follow-up: eight in the PV group and five in the sham group (Fig. 1).

Finally, 84% (76) of the patients from the PV group and 88% (76) of the patients from the sham group completed the 1-year spine X-ray follow-up. The median follow-up for imaging was 12 months (IQR = 12–12). The median duration between the onset of local back pain and initial imaging was 30 days in the PV group (IQR = 15–42) and 23 days in the sham group (IQR = 15–36). After the diagnostic radiography, PV took place at a median of 13 days (interquartile range 7–18 days) and the sham procedure at a median of 11 (7–17) days. The median time from symptoms onset to treatment was 43 days (interquartile range 29–52 days) in the PV group and 36 (24–51) days in the sham procedure group. The baseline characteristics of both groups were similar (Table 1).

Most of the OVCFs were moderate wedged or biconcave and located at the thoracolumbar level. In the PV group 48.9% of the fractures occurred spontaneously (no history of increased force on the spine), 18.9% after a

Table 1 Baseline characteristics

Characteristics	PV group (N = 90)	Sham group (N = 86)
Mean (SD) age (years)	74.7 (10.7)	76.9 (8.1)
Women	67 (74%)	66 (77%)
Median (interquartile range) number of days with back pain before procedure	43 (29–52)	36 (24–51)
Number of OVCFs at baseline	115	108
Mild (10–20%)[a]	37 (32%)	30 (28%)
Moderate (20–40%)	51 (44%)	49 (45%)
Severe (> 40%)	27 (23%)	30 (28%)
Wedge	56 (49%)	65 (60%)
Biconcave	59 (51%)	44 (40%)
Crush	0	0
Osteonecrosis	24	18
Vertebral level with bone oedema		
Th5-Th10	36 (31%)	24 (22%)
Th11-L2	59 (51%)	69 (64%)
L3-L5	20 (17%)	15 (14%)
No. of spinal levels treated[b]		
1	70 (61%)	66 (61%)
2	15 (26%)	15 (28%)
3	5 (13%)	4 (11%)
Bone density T score	− 2.4 (1.0)	− 2.4 (0.9)
Initial VAS score[c]	7.7 (1.4)	7.9 (1.6)

Values are numbers (percentages) unless stated otherwise

[a]Genant classification

[b]1—one vertebral fracture with bone oedema treated; 2—two vertebral fractures with bone oedema treated; 3—three vertebral fractures with bone oedema treated

[c]VAS = visual analogue score on a scale of 0–10

minor trauma (fall from a standing height or less or a fracture that occurred during daily activities such as lifting a heavy object), and 18.9% after a significant trauma (motor vehicle accident, sports-related accident, fall from a considerable height). In the sham group 38.4% of the fractures occurred spontaneously, 22.1% after a minor trauma, and 22.1% after a significant trauma. These proportions did not differ significantly between treatment groups ($\chi^2(3) = 2.037$, $p = 0.565$). Twenty-four patients (26.7%) from the PV group and 17 patients (19.8%) from the sham group had osteonecrosis at the treated level diagnosed on baseline MRI. These proportions did not differ between groups ($\chi^2(1) = 1.171$, $p = 0.279$, OR = 1.48, 95%CI = 0.73–2.99).

In the PV group 90 patients received PV for 115 vertebral bodies. In the sham group 86 patients were treated for 108 vertebral bodies. When more than one symptomatic fracture with bone oedema occurred in the same patient, all fractures were treated similar in 1 session. One hundred and thirty-six patients from both groups were treated for one fracture, 30 for two fractures, and 9 for three fractures.

Patients undergoing PV were treated with local anaesthetics exclusively, unless they required moderate sedation resulting in 50 micrograms Fentanyl being administered in 20/90 (22%) patients. Mean volume of cement placed was 5.11 mL (SD 1.81; range 1–11 mL). Cement volume did not differ between patients in the PV group with and without secondary fractures [$t(88) = 1.52$, $p = 0.133$]. Furthermore, cement volume did not significantly correlate with the number of new fractures in patients in the PV group, as indicated by Spearman's rho (r_s=0.129, $p = 0.226$). After applying a Bonferroni correction for six correlation analyses at each follow-up measurement, cement volume did not significantly predict the VAS scores at any of the time points.

Post-procedural CT scans demonstrated cement leakage in 105 of 115 treated vertebrae (91.3%). Leakage type 1 occurred in 20% of cemented vertebral bodies, type 2 in 15%, type 3 in 10%, type 4 in 39%, type 5 in 7%, and type 6 in 8%. All cement leakages were asymptomatic. The volume of injected cement was not significantly associated

with the frequency of cement leakage ($r_s = -.10$, $p = 0.347$).

In the PV group 24 patients were treated for a fracture with osteonecrosis and 17 in the sham group. The presence of osteonecrosis did not influence the differences between the PV and sham groups in VAS scores during follow-up, as assessed by a three-way interaction effect in the mixed model analysis between osteonecrosis, treatment group, and measurement occasion [$F(13, 711.94) = 0.374$, $p = 0.978$].

Five patients in the PV group and 4 patients in the sham group were treated for fractures at 3 levels. These subsets did not differ significantly with respect to their change in VAS scores over time [$F(6, 35.53) = 1.345$, $p = 0.263$].

New OVCFs During Follow-up

After a median follow-up of 12 months (IQR = 12–12) 31 new fractures were reported in 15 patients from the PV group and 28 new fractures in 19 patients from the sham group. The difference in incidence of new OVCFs was not significant [$F(1522) = 0.277$, $p = 0.600$]. The location of new OVCFs did not differ between the groups (Table 2). There was no higher fracture risk of adjacent versus distant vertebrae. Time to new OVCF is graphically displayed in Fig. 2. The presence of osteonecrosis was not associated with the occurrence of secondary fractures ($\chi^2(1) = 0.173$, $p = 0.678$).

From the 15 patients with new fractures in the PV group, 6 were symptomatic with bone oedema on MRI and received again PV at the new 13 fractured levels. From the 19 patients with new fractures in the sham group, 6 were symptomatic with bone oedema on MRI and received a sham procedure at the new 7 fractured levels.

Leakage into the disc above or below (type 1 and type 2) was not associated with more secondary fractures ($\chi^2(8) = 2.81$, $p = 0.946$).

The number of fractures at baseline was not associated with the number of new fractures over the 12-month follow-up ($\chi^2(12) = 16.521$, $p = 0.169$).

Occurrence of Height Loss in Treated Vertebra

Further height loss during follow-up of treated baseline OVCFs was observed in 7 (8%) patients in the PV group and 39 (45%) patients in the sham group ($\chi^2(1) = 28.85$, $p < 0.001$, OR = 9.84, 95%CI = 4.08–23.73). Severity grading of further height loss is displayed in Table 3. Time to the first occurrence of height loss is graphically displayed in Fig. 3. One patient from the sham group received an additional intervention at the treated level, because of persistent pain.

Adverse Events

There were two adverse events in the PV arm. One patient with COPD GOLD IV developed respiratory insufficiency after the procedure related to her underlying pulmonary disease. Another patient had a self-correcting vasovagal reaction.

Discussion

Our study demonstrated that further height loss of cemented vertebral bodies is prevented in nearly all patients after PV. Apparently, the treated vertebra is strengthened by the injected cement present in the vertebral body. In addition, only moderate vertebral height loss was noticed after PV compared to more severe height loss after sham intervention without cementation. Thus, cementation provides an important advantage in the prevention of morbidity associated with deterioration of posture such as severe kyphosis related to, for example, impaired pulmonary function and mortality [20, 21].

PV did not increase the risk of new vertebral fractures in the first year after treatment. There was no higher fracture risk of adjacent versus distant vertebral bodies. Thus, location of new OVCFs did not differ between groups. We found no risk factors after PV and sham for new fractures. The number of vertebral fractures at baseline, neither the presence of osteonecrosis nor cement leakage led to a

Table 2 Distribution of new OVCFs

Distribution of new OVCFs[a]	PV ($n = 31$)	Sham ($n = 28$)	Test for difference[b]	Odds ratio (95%CI)
Adjacent above	16 (52%)	14 (50%)	$\chi^2(1) = 0.02$, $p = 0.902$	1.07 (0.38–2.96)
Adjacent under				
Between (sandwich)	1 (3%)	1 (4%)	$\chi^2(1) = 0.005$, $p = 0.942$	0.90 (0.05–15.10)
Distant	14 (45%)	13 (46%)	$\chi^2(1) = 0.01$, $p = 0.922$	0.95 (0.34–2.65)

[a]A new OVCF was defined as a decrease of at least 4 mm in vertical dimension

[b]Chi-square test for crosstabs

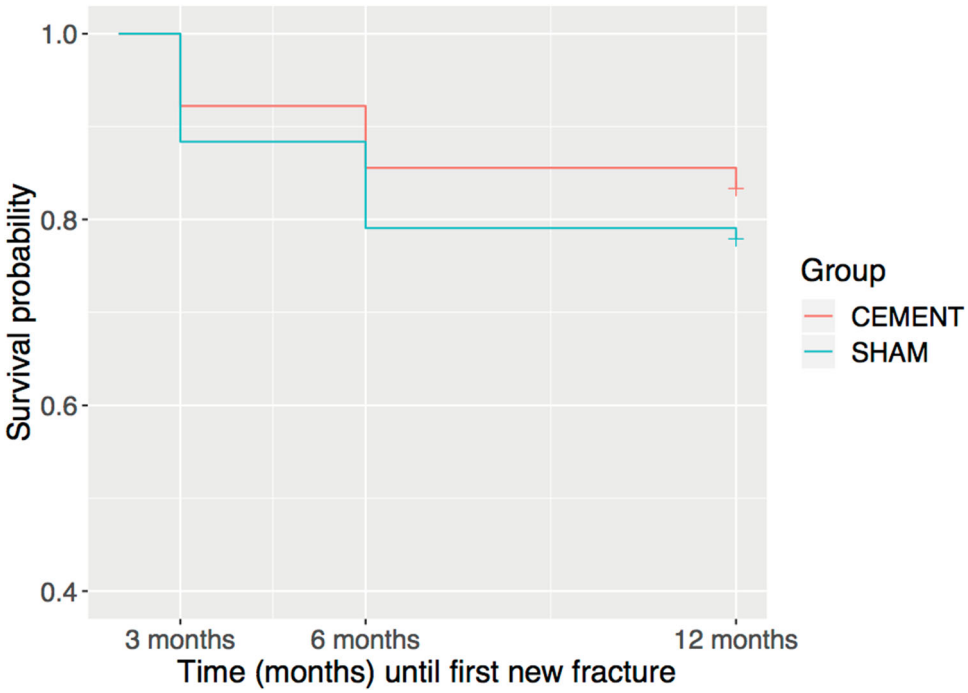

Fig. 2 Kaplan–Meier survival curves for time to first new fracture in both the cement and sham groups*. Patients lost to follow-up before having new fractures were excluded.
* Difference between curves of cement and sham groups is not statistically significant according to the log-rank test ($\chi^2(1) = 0.86$, $p = 0.353$)

Table 3 Height loss of the treated OVCF between baseline and last follow-up

Further height loss of treated vertebrae[a]	PV 115 treated vertebrae	Sham 109 treated vertebrae	Test for difference[b]	Odds ratio (95% CI)
None (0–3 mm)	106 (92%)	65 (60%)	$\chi^2(1) = 32.81$, $p < 0.001$	7.97 (3.65–17.40)
Moderate (4–7 mm)	9 (8%)	34 (31%)	$\chi^2(1) = 19.70$, $p < 0.001$	0.18 (0.08–0.41)
Severe (≥ 8 mm)	0 (0%)	10 (9%)	$\chi^2(1) = 11.00$, $p < 0.001$	0.04 (0.003–0.77)

[a]Further height loss during follow-up of treated baseline OVCFs with bone oedema was defined as height loss of 4 mm and more and categorised as moderate (4–7 mm) and severe (> 8 mm)

[b]Chi-square test for crosstabs

higher rate of new adjacent or distant vertebral fractures during the 12-month follow-up period.

The protective mechanical effect of cement has been reported by only few earlier (sham) RCTs comparing PV versus conservative management (pain medication, bed rest, and bracing) [12, 22]. Similar to our results, the VERTOS II RCT reported no progressive height loss in nearly all patients after PV as opposed to further vertebral body collapse in patients treated conservatively during 12-month follow-up [12]. Likewise, the VAPOUR sham RCT reported significant less vertebral height loss after PV with a 36% point difference in mean vertebral body height between the cemented (27%) and the control (63%) group [22].

Some non-controlled studies reported the risk of new vertebral fractures more often located adjacent to the cemented level [4, 6, 8, 23]. A possible explanation for having new fractures following vertebroplasty is the altered biomechanics in the treated area of the spine. Cement in an augmented vertebral body acts as a "pillar" that both reduces the normal inward bulge of the treated endplate and increases the stiffness of both the intervertebral joint and the whole motion segment. Contrary to the publications and hypothesis, our results showed no increased risk of a new vertebral fracture adjacent or distant to the cemented level. Likewise, a recently published review and one meta-analysis are sustaining this finding showing no increase in subsequent post-treatment fracture risk after cementation [24, 25]. As opposed to the VERTOS II trial

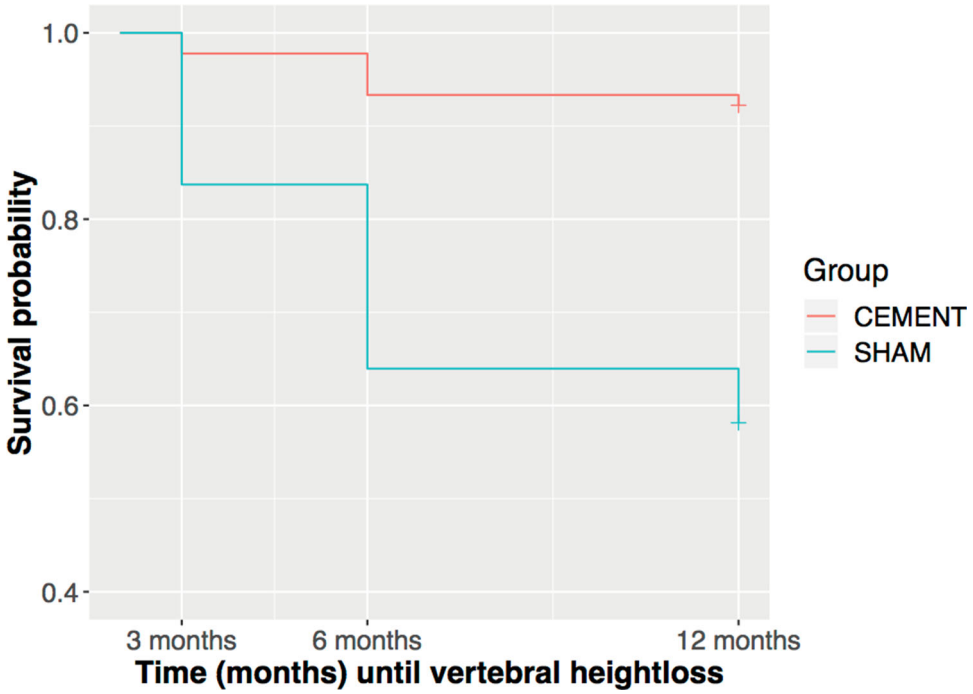

Fig. 3 Kaplan–Meier survival curves for time to first occurrence of height loss in both the cement and sham groups*. Patients lost to follow-up before having vertebral height loss were excluded. * Difference between curves of cement and sham groups is statistically significant according to the log-rank test ($\chi^2(1) = 27.93$, $p < 0.001$)

we did not find any risk factors for new adjacent or distant vertebral fractures. In VERTOS II, the only risk factor for the occurrence of new fractures was the number of OVCFs at baseline [12, 26]. We believe that the emergence of new OVCFs is caused by the ongoing osteoporosis disease only, and not due to the increased stiffness of the cemented vertebral body.

Cement leakage outside the vertebral body was seen in nearly all patients (92%) not causing symptoms as stated by previous research [27]. Higher volume of injected cement was not related to a higher incidence of leakage outside the vertebral body, nor is leakage linked to the occurrence of new fractures, contradictory to previous studies [28, 29]. Therefore, we believe a standard post-procedural CT seems no longer needed in routine daily practice, except in selected symptomatic cases related to the procedure [30].

The strength of these study results is thanks to the data derived from the VERTOS IV sham RCT with well-controlled homogeneous study groups comparing PV (with cementation) versus a sham intervention (no cementation) [31]. As opposed to many small non-randomised studies mostly lacking a control arm, these VERTOS IV-derived results provide more robust data with useful information regarding the chance of the occurrence and incidence of further height loss and secondary adjacent or distant fractures.

Limitations of this study include the fact that not all imaginable risk factors for fracture in patients with osteoporosis were investigated (e.g. body mass index, smoking, and collagen disease). All participants underwent the classic PV procedure in the cementation group. As such, the study has limited generalisability to other forms of augmentation and therefore cannot be extrapolated to balloon kyphoplasty, radiofrequency kyphoplasty, instrumented vertebroplasty or kyphoplasty, and non-balloon cavity creation kyphoplasty. In addition, the VERTOS IV results only apply to acute OVCFs (< 6 weeks) and may for that reason not be used for older, chronic vertebral fractures or in case of any underlying malignancy. 156 patients declined participation, but no screening logs were kept for these patients. This can suggest a selection bias towards recruitment of patients with lesser degrees of pain and disability.

Like VERTOS IV, most previous RCTs comparing PV with sham intervention used pain relief as the primary objective [22, 26, 31–33]. This topic remains of paramount importance. But, despite the abundant literature addressing this topic of pain, conflicting results have not contributed to the reduction of worldwide discussions and differences of opinion. We believe it is time to change course and also pay attention to other aspects related to OVCFs and PV. Our study concluded that no cementation leads to significant vertebral height loss with progressive kyphosis and change of posture. Based on these study results with the protective effect of PV on vertebral height, we consider posture in relation to morbidity and mortality a relevant item. This assumption is supported by previous publications on the relationship between posture and morbidity and mortality [20, 21] and demands more attention and

warrants further research. Moreover, analyses of insurance claims data revealed lower mortality and morbidity rates for patients who underwent cementation versus conservative therapy [34].

Conclusion

The risk of further vertebral height loss is significantly lower after PV compared to a sham intervention, i.e. PV protects against progressive vertebral height loss. In addition, PV does not increase the risk of new adjacent and distant OVCFs.

Authors Contribution CEF and PNML had full access to all the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis, and act as guarantors. PNML, CAHK, JdV, MCS, AJS, JRJ, ED, OEHE, and FHJ designed the study. IVDH, MB, and KS gathered the data. PNML, MCS, AJS, CAHK, OEHE, and FHJ performed the procedures. PL and JdV analysed the data. CEF and AV undertook morphometric measurements. CEF, PNML, AV, JdV, and PL wrote the first draft, and all the contributors made the decision to submit the manuscript for publication.

Funding This study was supported by Stryker (Grant No. S-I-013). The sponsor had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Availability of Data and Materials The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

Conflict of interests The authors declare that they have no competing interest.

Ethics Approval and Consent to Participate The procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This trial was an institutional review board-approved sham-controlled, double-blind, multicentre, randomised trial performed at four community hospitals in the Netherlands (MN-11-004, approval protocol 1055).

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