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ORIGINAL RESEARCH • MUSCULOSKELETAL IMAGING

Vertebroplasty versus Active Control Intervention for Chronic Osteoporotic Vertebral Compression Fractures: The VERTOS V Randomized Controlled Trial

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Conflicts of interest are listed at the end of this article.

See also the editorial by Beall and De Leacy in this issue.

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Background: Evidence regarding percutaneous vertebroplasty (PV) for chronic painful osteoporotic vertebral compression fractures (OVCFs) remains limited.

Purpose: To compare pain relief, quality of life, and disability between PV and active control (anesthetic infiltration) interventions for chronic OVCF.

Materials and Methods: This prospective randomized clinical trial was conducted between May 2013 and June 2019 in participants with pain due to OVCF lasting longer than 3 months with bone marrow edema present at MRI. Study participants were randomly assigned to undergo PV (n = 40) or active control intervention (n = 40). The primary outcome was pain severity, assessed with the visual analog scale (VAS) (range, 0–10) during 12 months after treatment. Secondary outcomes included Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) score (range, 0–100) and Roland Morris Disability Questionnaire (RMDQ) score (range, 0–100). Outcomes were analyzed according to a longitudinal multilevel model used to test the difference between groups in change from baseline across follow-up.

Results: The mean age of the 80 participants (54 women) was 69 years ± 10 (SD) in the PV group and 71 years ± 10 in the active control group. VAS score was 7.6 (95% CI: 7.0, 8.2) in the PV group and 7.3 (95% CI: 6.9, 7.8) in the active control group at baseline (P = .47) and 3.9 (95% CI: 3.1, 4.8) and 5.1 (95% CI: 4.3, 6.0), respectively, at month 12 (P = .045). At month 12, the group difference from baseline was 1.3 (95% CI: 0.1, 2.6; P = .02) for VAS, 5.2 (95% CI: 0.9, 9.4; P = .02) for QUALEFFO, and 7.1 (95% CI: −3.3, 17.5; P = .18) for RMDQ, favoring the PV group.

Conclusion: In the treatment of pain caused by chronic OVCFs, PV is more effective for pain relief and quality of life improvement than anesthetic injection alone, with similar improvement for disability between the groups.

Clinical trial registration no. NCT01963039

Vertebral compression fractures are the most common complication of osteoporosis and can result in long-term morbidity and mortality (1,2). Standard care in patients with a painful osteoporotic vertebral compression fracture (OVCF) is conservative therapy. Percutaneous vertebroplasty (PV) involves polymethylmethacrylate injection into the vertebral body (3–5).

Randomized controlled trials (RCTs) have provided conflicting results regarding the effectiveness of PV in patients with acute (fracture age ≤6 weeks) OVCFs: Two *New England Journal of Medicine* RCTs comparing PV versus sham intervention showed no benefit of PV (6,7). An unmasked RCT (VERTOS II, comparing PV vs conservative therapy) and one sham RCT (VAPOUR, comparing PV vs sham intervention) found effective pain relief (8,9). Moreover, two sham RCTs (VAPOUR and VERTOS IV, comparing PV vs sham intervention) showed better protection of vertebral body height after PV in patients with acute OVCFs (9,10).

Only one unmasked RCT has compared clinical results of PV and conservative therapy in chronic OVCFs. The results showed that PV led to a significant improvement in visual analog scale (VAS) scores, Oswestry Disability Index scores, and Roland Morris Disability Questionnaire (RMDQ) scores (11). To date, no blinded RCT exists for chronic (>3 months) OVCFs, to our knowledge (12).

VERTOS II suggested that patients with continuing pain at 3 months after an acute OVCF could benefit from PV (13). VERTOS IV showed that a substantial proportion of patients in the control arm continued to have disabling pain at 12-month follow-up (14).

Considering limited data on PV in chronic OVCFs and persisting pain scores (VAS score ≥4) observed in 40% of patients in the control group at short- (3-month) and

Abbreviations

OVCF = osteoporotic vertebral compression fracture, PV = percutaneous vertebroplasty, QUALEFFO = Quality of Life Questionnaire of the European Foundation for Osteoporosis, RCT = randomized controlled trial, RMDQ = Roland Morris Disability Questionnaire, VAS = visual analog scale

Summary

In a randomized trial of participants with chronic vertebral compression fractures, percutaneous vertebroplasty led to superior pain reduction and quality of life improvement over 12 months versus active control (anesthetic infiltration).

Key Results

- In a prospective randomized controlled trial, 80 participants with chronic (>3 months) vertebral compression fracture underwent either percutaneous vertebroplasty (PV) (n = 40) or anesthetic infiltration alone (active control) (n = 40).
- At 12 months, there was greater pain reduction (P = .02) and greater improvement in health-related quality of life (P = .02) in the PV group compared with the active control group, with similar improvement in disability (P = .18) between the groups.

midterm (12-month) follow-up, the VERTOS research group decided to perform the VERTOS V study (11,13). On the basis of our hypothesis that this subgroup of patients with chronic painful OVCFs could benefit from PV, we conducted this RCT. The purpose was to compare pain relief and quality of life in patients with chronic painful OVCFs who underwent either percutaneous PV or active control intervention.

Materials and Methods

Study Participants and Design

In this single-center RCT, patients with painful chronic OVCFs were recruited for enrollment. Recruitment took place from May 2013 through June 2019. Inclusion criteria were *(a)* age of 50 years or older; *(b)* focal back pain (score of 5 or higher on the VAS) at the level of the OVCF for at least 3 months at the time of spinal radiography; *(c)* one or more OVCFs on spinal radiograph with vertebral height loss of 15% or more between the fifth thoracic vertebra and fifth lumbar vertebra; *(d)* diminished bone density (T score less than −1) on dual-energy x-ray absorptiometry scan; and *(e)* bone edema of the fractured vertebra at MRI. An internist performed physical examinations and provided independent validation of focal back pain with a VAS score of 5 or higher at the level of the OVCF before randomization. Exclusion criteria were severe cardiopulmonary condition, untreatable coagulopathy, or suspected underlying disease (Fig 1).

We performed a blinded sham RCT at Elisabeth Tweesteden Ziekenhuis Hospital in the Netherlands. Eighty participants were randomized by computer in a block size of six, with a randomization ratio of 1:1. One day after the intervention, participants were asked to guess which procedure they had undergone. All adverse events were recorded.

Participants, internists, and outcome assessors were blinded and remained so during the 12 months of follow-up. Crossover between study groups was not allowed.

Ethics Statement

The protocol was approved by the institutional review board medical ethical committee, and union privacy rules were followed. The study was registered at ClinicalTrials.gov and can be accessed online using the identifier NCT01963039. All participants gave written informed consent to take part in the trial.

Image Acquisition Protocols and Interpretation

Images of the OVCFs in the thoracolumbar spine were obtained with conventional radiography equipment (DigitalDiagnost, Philips) in anteroposterior and lateral projections. Assessment of the OVCFs was based on the Genant classification (15). Bone edema was defined as increased signal intensity on short-tau inversion-recovery MRI scans acquired using an MRI system (Ingenia 1.5 T, Philips). Vertebral fracture clefts were defined as a circumscribed area, a fluid cleft with high signal intensity at T2-weighted MRI.

The intervention took place in the angiography suite of the Department of Radiology with the biplane illumination system AlluraClarity (Philips). Transpedicularly placed 11- or 13-gauge needles (Osteo-site bone biopsy needle, Cook Medical) were used in participants in both the PV and active control groups. Polymethylmethacrylate cement (VertaPlex HV bone cement, Stryker) was introduced into the vertebral body of PV participants through needles with use of a mixer and delivery system (AutoPlex, Stryker). Participants in the PV group underwent CT (256–multidetector section CT, Philips) immediately after the procedure to record the distribution of the cement; this was simulated in the placebo group. Control radiographs of the thoracolumbar spine were obtained at 3-, 6-, and 12-month follow-up (DigitalDiagnost, Philips).

Primary and Secondary Outcome Measures

The primary objective was to compare PV- and active control–treated groups to determine the difference in mean pain reduction based on VAS score during 12-month follow-up (16). The secondary objectives were to determine the differences between groups in mean changes of health-related quality of life (Quality of Life Questionnaire of the European Foundation for Osteoporosis [QUALEFFO]) and physical functioning (RMDQ) during 12-month follow-up (17,18). For both primary and secondary outcomes, participant data were collected at 1 week and 1, 3, 6, and 12 months.

Additional data were extracted from the electronic health records, including vertebral height loss of treated fractures (defined as ≥4 mm), new fractures (adjacent or remote), cement volume, complications, and use of analgesics.

Interventions

PV and active control group participants underwent subcutaneous infiltration with 5 mL 1% lidocaine at the vertebral level followed by periosteal pedicle infiltration with 5 mL 0.25% bupivacaine. Straight needles (11- or 13-gauge) were positioned trans- or bipedicular for PV or periosteal for the active control intervention. Polymethylmethacrylate cement was prepared using the AutoPlex mixing and delivery system, and cement mixing was performed in the procedural suite. Because

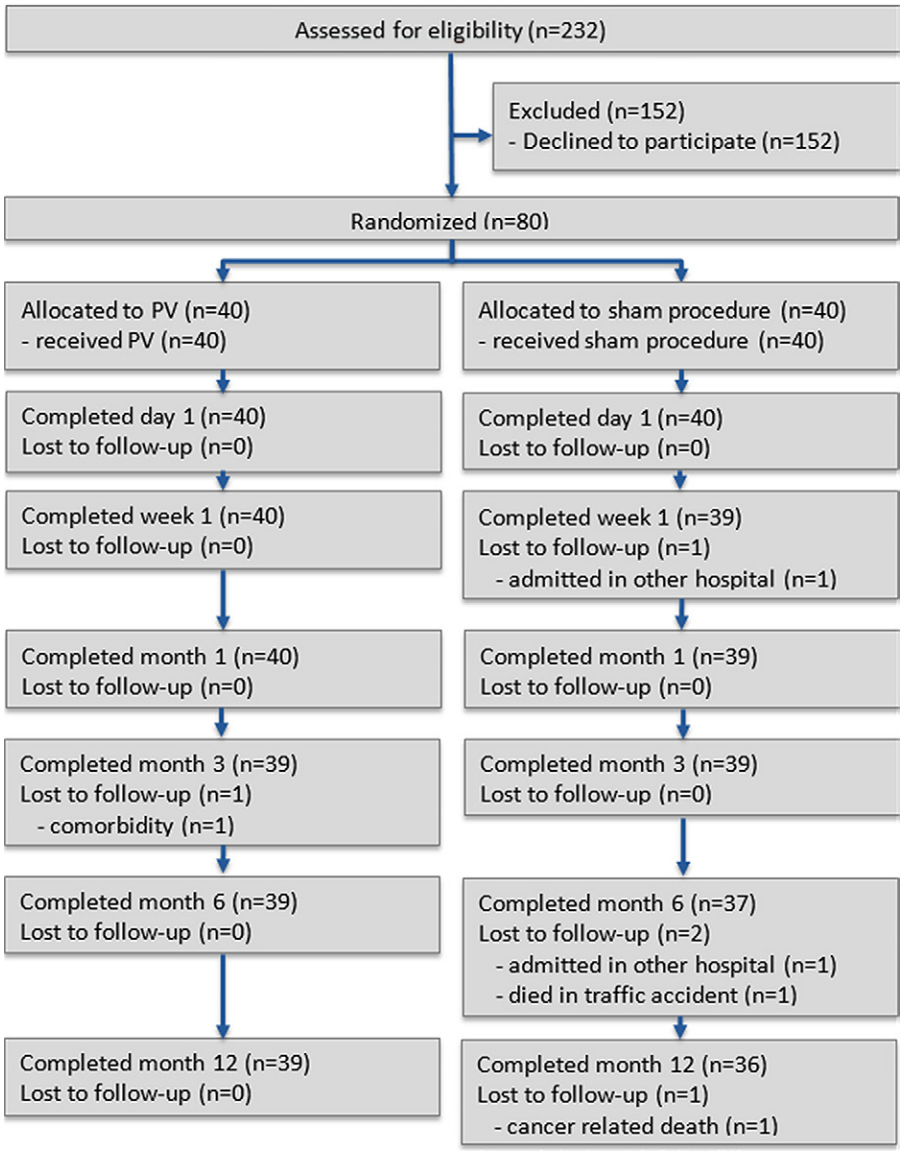

Figure 1: Flow diagram of study participants. PV = percutaneous vertebroplasty.

participants could become aware of their treatment assignment due to mixing sounds and cement odor, cement was prepared for both groups but not used for the active control group. In the active control group, the injection phase was simulated using verbal and physical cues. Treatment of new OVCFs was per the initial assignment.

Additional analgesics were allowed at intake or follow-up and categorized according to the World Health Organization classification (19).

Statistical Analysis

All statistical analyses were performed by P. Lodder. Sample size calculation was performed using an online power analysis tool for longitudinal mixed-effects models *(http://www.rmass.org)*. Assuming 5% attrition at each follow-up measure and given a significance level of .05, random intercept variance of 1, random slope variance of 0.5, error variance of 1, and an expected three-point difference between the treatments in the VAS score at the last time point, the required sample size to acquire a power of 0.80 is 78 (39 in each treatment group).

Analysis was by intention to treat. We used χ^2 tests to compare the proportions of adverse events, drugs, and baseline fractures. For continuous variables, we assessed whether they were normally distributed using the Kolmogorov-Smirnov test. For continuous and normally distributed variables, we computed means and SDs, whereas for nonnormally distributed variables, we reported the medians and IQRs.

Linear mixed modeling was used to analyze our primary and secondary end points. A longitudinal multilevel model was fit to the data, including both a random intercept and slope to take into account differences between participant outcomes over time. The full information maximum likelihood procedure allowed for analysis of all available data from each participant despite the occasional missing observation or dropout, assuming the data were missing at random. In the mixed model analysis, our research questions were investigated using the interaction effect between

treatment group and time. A categorical time variable coding (0 = baseline; 1 = day 1; 2 = week 1; 3 = months 1–12) was used to model the nonlinear changes in the outcomes across time. Model estimates were adjusted based on the covariates of age, sex, vertebral level, pain treatment, fracture cleft, new fractures after baseline, and progressive loss of vertebral height. Analyses to determine whether cement volume correlated with VAS score change was carried out using the Pearson correlation coefficient. Analyses were performed using SPSS (version 23, IBM) and the R programming software (version 4.1.1, R Development Core Team). Two-tailed $P < .05$ was considered to indicate statistically significant difference.

Results

Participant Characteristics

In total, 232 patients with at least one thoracolumbar fracture met all inclusion criteria (Fig 1). After assessment for eligibility, 152 patients declined to participate. The remaining 80 patients were randomly allocated, resulting in 40 participants with 72 fractures in the PV group (mean age, 69 years ± 10 [SD]; 27 women, 13 men) and 40 participants with 63 fractures in the active control group (mean age, 71 years ± 10 [SD]; 27 women, 13 men). In the PV group, one participant was lost to follow-up after 3 months due to comorbidity unrelated to treatment and subsequent inability to continue follow-up. In the active control group, two participants were lost to follow-up after completing 1-week and 6-month follow-up. Two participants in the active control group died after 6 and 12 months due to a traffic accident and cancer. The median number of days between local back pain onset and diagnosis was 38 and 67 in the PV and active control groups, respectively. The median number of days with pain before the procedure was 176 and 185 for the PV and active control groups, respectively. Fracture type, location, and severity are depicted in Table 1, with distribution of fracture types according to the Genant classification. Most vertebral fractures were wedge-shaped and particularly localized in the thoracolumbar junction. These OVCFs were predominantly single-vertebral fractures.

Comparison of PV and Active Control Group Pain, Quality of Life, and Physical Functioning Scores over Time

Compared with baseline, a reduction in VAS score was observed in both groups at all measurement points during the 12-month period. In the PV group, mean VAS scores decreased from 7.6 at baseline to 5.1, 4.5, 4.0, 3.5, 3.9, and 3.9 at 1 day, 1 week, and 1, 3, 6, and 12 months, respectively (all $P < .001$). In the active control group, mean VAS scores decreased from 7.3 at baseline to 4.7, 5.0, 4.9, 4.9, 4.9, and 5.1 (all $P < .001$).

For VAS score, there was a significant interaction effect between treatment group and measurement time point (Table 2). Both groups showed a significant decrease in mean VAS score at follow-up. However, this decrease was stronger in the PV than in the active control group, indicating that the relationship between VAS score and time is dependent on treatment group (Fig 2). From baseline to 12 months, the mean VAS score declined by 3.6 (95% CI: 2.7, 4.6) in the PV group and 2.3 (95%

Table 1: Baseline Characteristics of Participants

Characteristic	Active Control Group (n = 40)	Vertebroplasty Group (n = 40)
Mean age (y)*	71 ± 10	69 ± 10
Sex		
F	27 (68)	27 (68)
M	13 (32)	13 (32)
No. of days with pain before procedure†	185 (68–1165)	176 (43–907)
Cardiovascular comorbidity	11 (28)	8 (24)
Pulmonary comorbidity	5 (13)	10 (26)
Fracture details		
No. of VCFs at baseline	63	72
Genant classification		
Mild	22/63 (35)	33/72 (46)
Moderate	23/63 (37)	18/72 (25)
Severe	18/63 (29)	21/72 (29)
Type of fracture		
Wedge	43/63 (68)	57/72 (79)
Biconcave	20/63 (32)	15/72 (21)
Vertebral level		
T4–T10	18 (45)	7 (18)
T11–L2	27 (68)	32 (80)
L3–L5	4 (10)	9 (23)
No. of spinal levels treated		
1	20 (50)	28 (70)
2	11 (28)	4 (10)
3	7 (18)	5 (13)
4	1 (3)	2 (5)
5	1 (3)	1 (3)
Medication		
Nonopioids‡	28 (70)	32 (80)
Weak opioids§	5 (13)	10 (25)
Strong opioids‖	9 (23)	16 (40)
Acenocoumarol	8 (20)	2 (5)
Drugs for osteoporosis	28 (70)	28 (70)
Baseline scores*		
Bone density T score	−2.0 ± 1.1	−2.0 ± 1.3
Initial VAS score#	7.3 ± 1.5	7.6 ± 1.8
QUALEFFO score**	60.9 ± 8.8	61.8 ± 9.3
RMDQ score††	63.4 ± 17.9	64.7 ± 20.0

Note.—Unless otherwise stated, data are numbers of participants, with percentages in parentheses. Opioid classification is from the World Health Organization analgesic ladder. QUALEFFO = Quality of Life Questionnaire of the European Foundation for Osteoporosis, RMDQ = Roland Morris Disability Questionnaire, VAS = visual analog scale, VCF = vertebral compression fracture.

* Data are means ± SDs.

† Data are medians, with ranges in parentheses.

‡ Paracetamol, nonsteroidal anti-inflammatory agents, etc.

§ Codeine, tramadol, etc.

‖ Morphine, fentanyl, etc.

Score ranges from 0 (no pain) to 10 (worst pain ever).

** Score ranges from 0 to 100, with higher scores indicating worse quality of life.

†† Score ranges from 0 to 100, with higher scores indicating worse physical functioning.

Table 2: Fixed Effect Estimates Resulting from the Linear Mixed Models Used to Test the Main Hypotheses That the Treatment Groups Differ in Their Change over Time (Time*Group Effect) on the Primary and Secondary End Points, Adjusted for Theoretically Important Covariates

	VAS		QUALEFFO		RMDQ	
Term or Covariate	Test Statistic	*P* Value	Test Statistic	*P* Value	Test Statistic	*P* Value
Standard model terms						
Intercept	$F_{1,67.1} = 15.2$	<.001*	$F_{1,66.9} = 47.51$	<.001*	$F_{1,69.1} = 16.62$	.004*
Time	$F_{3,345.3} = 54.45$	<.001*	$F_{3,298} = 14.44$	<.001*	$F_{3,290.7} = 24.53$	<.001*
Group	$F_{3,345.3} = 4.46$	.88	$F_{3,297.9} = 2.2$	.42	$F_{3,290.7} = 2.61$	.67
Time*group	$F_{1,67.1} = 15.2$	.004*	$F_{1,66.9} = 47.51$	.09	$F_{1,69.1} = 16.62$	.05
Theoretically important covariates						
Age	$F_{1,67.2} = 0.34$	.56	$F_{1,66.5} = 0.21$	.65	$F_{1,69} = 0.39$	.53
Sex	$F_{1,67.8} = 1.82$	.18	$F_{1,65.6} = 8.29$	.005	$F_{1,68.3} = 4.56$	.04
Height loss	$F_{1,67.2} = 0.03$	.86	$F_{1,64.9} = 3.27$	.08	$F_{1,67.1} = 1.48$	.23
New fractures	$F_{2,67.5} = 0.68$	.51	$F_{2,73} = 0.43$	.65	$F_{2,73.1} = 0.35$	.71
Fracture cleft	$F_{1,68.8} = 0.63$	.43	$F_{1,67} = 11.54$	<.001	$F_{1,67.7} = 1.44$	.24
Nonopioid use	$F_{1,67.1} = 0$	.98	$F_{1,65.4} = 1.04$	.31	$F_{1,68.1} = 0.52$	.47
Weak-opioid use	$F_{1,67} = 3.36$	.07	$F_{1,65.8} = 0.01$	.94	$F_{1,67.3} = 0.12$	.73
Strong-opioid use	$F_{1,67.3} = 0.24$	.63	$F_{1,66.1} = 1.94$	.17	$F_{1,68.2} = 2.29$	.14

Note.—The time*group row indicates the effect used to test the primary (visual analog score [VAS]) and secondary (Quality of Life Questionnaire of the European Foundation for Osteoporosis [QUALEFFO] and Roland Morris Disability Questionnaire [RMDQ]) end points.
* $P < .05$.

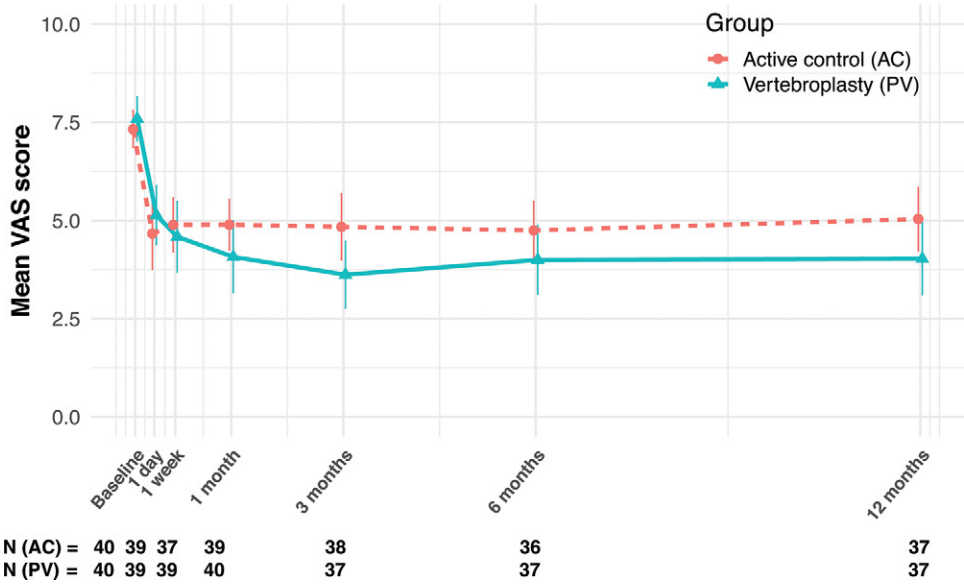

Figure 2: Mean visual analog scale (VAS) score for the PV and active control groups over 12-month follow-up. Interaction plot shows that the PV group had a larger decrease in VAS score across follow-up than the active control group. The vertebroplasty group is represented by the blue line (triangular points), and the active control group is represented by the red (round points). Whiskers indicate 95% CIs.

CI: 1.4, 3.3) in the active control group. Table 3 indicates that PV participants had a significantly larger reduction in VAS scores over 12 months than active control group participants (mean VAS score difference over 12 months, 1.3 [95% CI: 0.1, 2.6]; $P = .02$).

A similar pattern of improvement was observed for the QUALEFFO scores. Table 3 indicates a significant difference between groups in the change across the 12-month follow-up ($P = .02$), suggesting that the groups differed in their QUALEFFO score improvement over the 12-month follow-up. Although the score reduction is similar between the groups up to 1 month after baseline, thereafter, the lines start to diverge, with a plateau for sham and a further decline for PV (Fig 3). Both groups showed an improvement in RMDQ score during 12-month follow-up, but no difference was observed between the PV and active control group.

Table 3: Primary and Secondary Outcomes according to Group and Timing

Outcome and Time Period	Vertebroplasty (n = 40)	Active Control (n = 40)	Group Difference*	P Value
VAS score				
Baseline	7.6 (7.0, 8.2)	7.3 (6.9, 7.8)	−0.3 (−1.0, 0.5)	.47
1 day	5.1 (4.3, 5.9)	4.7 (3.9, 5.5)	−0.4 (−1.5, 0.8)	.50
1 week	4.5 (3.8, 5.2)	5.0 (4.3, 5.8)	0.6 (−0.5, 1.6)	.30
1 month	4.0 (3.3, 4.8)	4.9 (4.1, 5.7)	1.0 (−0.1, 2.0)	.08
3 months	3.5 (2.7, 4.4)	4.9 (4.1, 5.7)	1.4 (0.2, 2.5)†	.02†
6 months	3.9 (3.1, 4.7)	4.9 (4.1, 5.6)	1.0 (−0.1, 2.1)	.09
12 months	3.9 (3.1, 4.8)	5.1 (4.3, 6.0)	1.2 (0.0, 2.4)†	.045†
Difference from baseline to 12 months	3.6 (2.7, 4.6)†	2.3 (1.4, 3.3)†	1.3 (0.1, 2.6)†	.02†
QUALEFFO score				
Baseline	56.3 (53.1, 59.5)	55.3 (52.1, 58.4)	−1.0 (−5.5, 3.5)	.65
1 week	51.3 (48.9, 53.6)	52.7 (50.4, 55.0)	1.4 (−1.9, 4.8)	.39
1 month	48.6 (46.2, 51.0)	51.5 (49.1, 53.9)	2.9 (−0.5, 6.3)	.10
3 months	48.0 (44.7, 51.3)	52.1 (48.9, 55.4)	4.1 (−0.5, 8.8)	.08
6 months	48.6 (45.9, 51.4)	51.4 (48.7, 54.2)	2.8 (−1.1, 6.7)	.16
12 months	47.9 (44.9, 50.9)	53.1 (50.2, 56.0)	5.2 (1.0, 9.4)†	.02†
Difference from baseline to 12 months	7.5 (4.2, 10.8)†	2.3 (−0.3, 5.0)	5.2 (0.9, 9.4)†	.02†
RMDQ score				
Baseline	64.7 (58.5, 70.9)	63.8 (57.6, 70.0)	−0.9 (−9.7, 7.8)	.84
1 week	55.0 (49.5, 60.5)	56.1 (50.5, 61.7)	1.1 (−6.7, 8.9)	.78
1 month	44.6 (38.2, 51.1)	52.3 (45.8, 58.8)	7.7 (−1.5, 16.9)	.10
3 months	42.6 (35.8, 49.4)	52.8 (46.2, 59.5)	10.2 (0.7, 19.8)†	.04†
6 months	45.2 (37.7, 52.6)	48.7 (41.4, 56.0)	3.5 (−6.9, 14.0)	.50
12 months	42.0 (34.8, 49.2)	49.0 (41.7, 56.3)	7.0 (−3.2, 17.3)	.18
Difference from baseline to 12 months	21.7 (14.3, 29.2)†	14.6, (7.4, 21.9)†	7.1 (−3.3, 17.5)	.18

Note.—Unless otherwise specified, data are means, with 95% CIs in parentheses. Estimated means at follow-up measurements are adjusted for baseline differences. Visual analog scale (VAS) scores range from 0 (no pain) to 10 (worst pain). Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) scores range from 0 (best quality of life) to 100 (worst quality of life). Roland Morris Disability Questionnaire (RMDQ) scores range from 0 (highest physical functioning) to 100 (lowest physical functioning). Results show statistical significance in favor of vertebroplasty at 12 months for the VAS and QUALEFFO scores.

* A positive group difference indicates worse mean scores in the active control group.

† $P < .05$.

Comparison of Additional Outcome Measures in the PV and Active Control Group

Figure 4 shows the change in use of analgesics over the 12-month follow-up in both groups. In the PV group, at baseline, 40% of the participants (16 of 40) received strong opioids; 25% (10 of 40), weak opioids; and 80% (32 of 40), nonopioids. At the 12-month follow-up, strong-opioid use decreased significantly to 17% (six of 35 participants) (P = .04), weak-opioid use to 5.9% (two of 34 participants) (P = .03), and nonopioid use to 54% (19 of 35 participants) (P = .04). In the active control group, at baseline, 23% of the participants (nine of 40) received strong opioids; 13% (five of 40), weak opioids; and 70% (28 of 40), nonopioids. At the 12-month follow-up, strong-opioid use was similar at 14% (five of 35 participants) (P = .72), weak-opioid use at 8.6% (three of 35) (P = .72), and nonopioid use at 60% (21 of 35) (P = .25). Between baseline and the 12-month follow-up, the percentage of participants with no medicine intake increased significantly in the PV group from 10% (four of 40) to 40% (14 of 35) (P = .02), while the increase in the active control group from 15% (six of 40) to 34% (12 of 35) did not reach statistical significance (P = .07). However, there were no significant differences between groups in these changes in medicine intake across time (strong opioids: P = .36; weak opioids: P = .26; nonopioids: P = .28; no medicine: P = .40).

In total, 135 fractures were treated (active control, 72; PV, 63), with 100% technical success. In the PV group, eight of the 63 treated fractures (13%) showed fracture cleft. In the active control group, six of the 72 treated fractures (8.3%) showed fracture cleft. In the PV group, eight of the 40 participants (20%) showed fracture cleft. In the active control group, five of the 40 participants (13%) showed fracture cleft. We found no evidence of a difference between groups in the occurrence of fracture cleft (P = .54). Furthermore, in a subgroup analysis, no difference was observed in terms of pain reduction after cementation between participants with a vertebral fracture versus those with a vertebral fracture cleft.

The mean cement volume used in the PV group was 5.8 mL ± 1.4 (SD) (range, 3.3–8.5 mL). Cement leakage was detected at CT in 70% of treated vertebrae. No correlation was observed between mean cement volume and VAS score change between baseline and 12-month follow-up (P = .08).

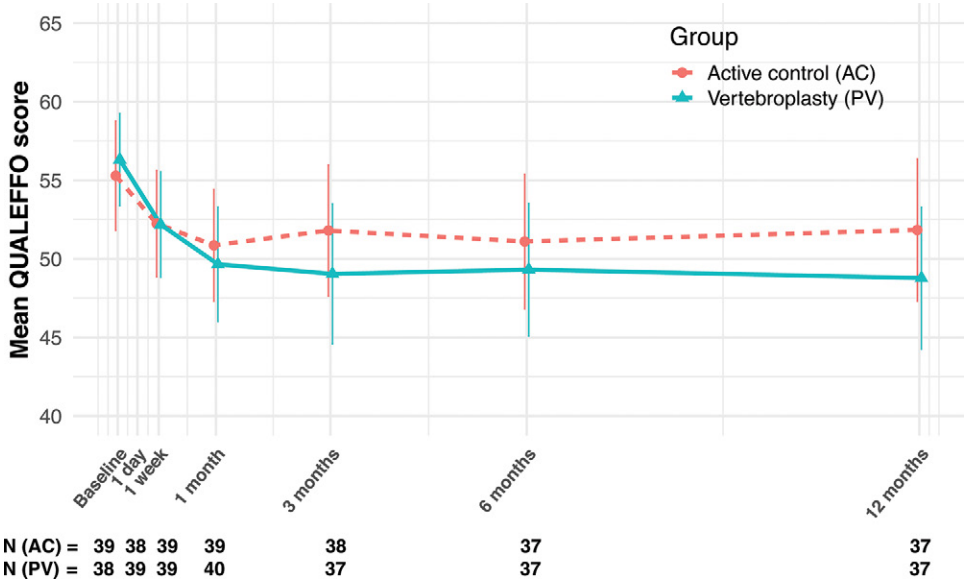

Figure 3: Health-related quality of life score for the PV and active control groups over 12-month follow-up. Interaction plot shows that the PV group had a larger decrease in Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) score across follow-up than the active control group. The vertebroplasty group is represented by the blue line (triangular points), and the active control group is represented by the red (round points). Whiskers indicate 95% CIs.

Serious adverse events related to OVCF occurred in one participant from the active control group, with spinal cord compression due to a progressively collapsed vertebral body. In both groups, most participants (94%) were convinced they received cementation. There were no crossovers in the trial.

Six participants in the active control group and seven in the PV group developed new fractures (remote or adjacent fractures) during the 12-month follow-up period, but this difference was found to be nonsignificant (P = .76). Progressive height loss was observed in four participants from the active control group but none in the PV group. A difference was not observed with the Fisher exact test (P = .12).

Discussion

Randomized controlled trials (RCTs) have provided conflicting results regarding the effectiveness of percutaneous vertebroplasty (PV) in patients with acute (fracture age, ≤6 weeks) osteoporotic vertebral compression fractures (OVCFs) (6–9). In chronic painful OVCFs, there is limited evidence to support the use of PV. Only one unmasked RCT, which compared PV and conservative therapy in chronic OVCFs, showed that PV led to a significant improvement in visual analog scale (VAS) scores and Roland Morris Disability Questionnaire (RMDQ) scores throughout follow-up (11). VERTOS II suggested that patients with continuing pain at 3 months after an acute OVCF could benefit from PV (13). VERTOS IV showed that a substantial proportion of participants in the control arm continued to have disabling pain at 12-month follow-up (14). In light of limited evidence on PV in chronic OVCFs and the persisting pain scores (VAS score ≥4) observed in 40% of participants in the control group during follow-up, the VERTOS research group decided to perform the VERTOS V study (11,13). The purpose of this RCT was to compare pain relief and health-related quality of life in patients with chronic painful OVCFs who underwent either PV or active control intervention. VAS score in the PV group was lower than in the active control group at both 3 months (PV, 3.5; control, 4.9 [P = .02]) and 12 months (PV, 3.9; control, 5.1 [P = .045]). During the 12-month period, the mean VAS score showed a greater overall decline in the PV group (3.6 [95% CI: 2.7, 4.6]) compared with controls (2.3 [95% CI: 1.4, 3.3]; P = .02). Improvement in Quality of Life Questionnaire of the European Foundation for Osteoporosis score was observed in the PV compared with active control group (PV, 7.5; control, 2.3 [P = .02]). The RMDQ scores also improved after intervention, but no difference was observed between the PV and active control group during 12-month follow-up.

Interpretation of prior blinded and open-label studies of PV has led to differing recommendations (20,21). The results of VERTOS V support the findings from open-label trials that PV has a role in the treatment of selected patients with persistent pain due to a chronic OVCF (6,7,9,14). Kaufmann et al (22) reported that patients who had developed fractures for up to 1 year before surgery had a good response to PV and showed improved pain relief and a better health-related quality of life. An unmasked RCT for patients with persistent severe local back pain caused by chronic OVCFs with 1-year follow-up comparing PV (n = 46) with nonsurgical management (n = 50) demonstrated better pain relief and functional outcomes after PV, as determined by VAS scores, Oswestry Disability Index scores, and RMDQ scores (all P < .001) (11). VERTOS V demonstrated a similar benefit of PV in selected patients. In contrast to those studies, this is the first blinded RCT, to our knowledge, comparing PV with active control intervention in chronic OVCFs. The VERTOS V study demonstrated

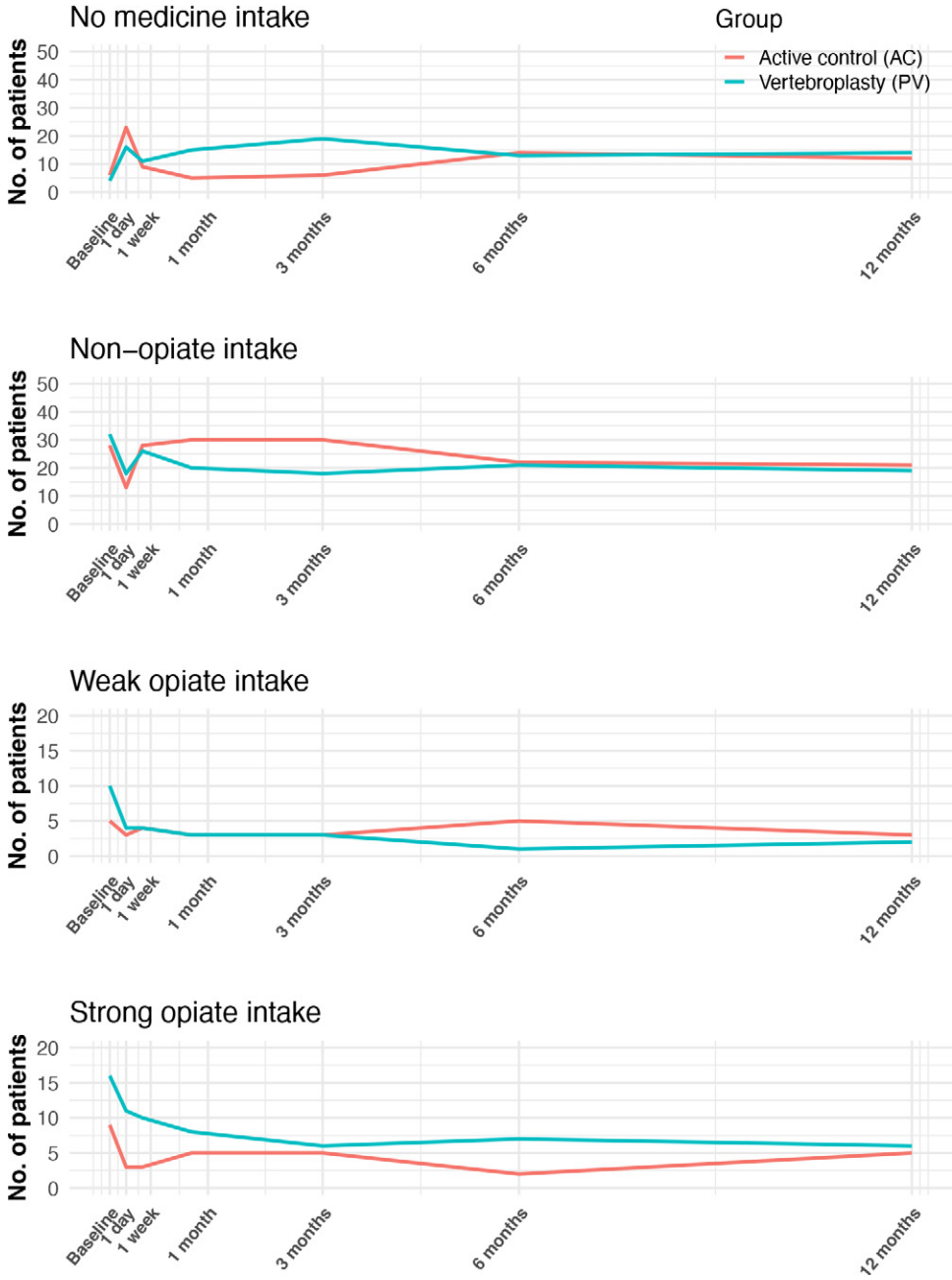

Figure 4: Line graphs show the use of analgesics by participants in the active control and percutaneous vertebroplasty groups over 12-month follow-up.

that, with stringent selection and proven bone edema, PV offered added value in pain management and quality of life. The results from Chen et al (11) for chronic OVCFs were even better, with significant clinical improvements. The increased pain relief after PV remained significant throughout the year of follow-up. This is remarkable, since fracture healing in the conservative treatment group should be complete within several months. However, some patients in the conservative treatment group continued to develop chronic back pain, possibly as a result of nonhealing of the fracture. When combining the results of previous VERTOS II and IV trials, we also found that significantly more patients in the sham and conservative group had a high pain score (VAS score ≥5) at 12-month follow-up than those in the PV group (40.1% vs 20.7%). Five predictors for sustained high local back pain were identified: female sex, patients with a baseline VAS score greater than 8, pain duration longer than 3 weeks until treatment, mild or severe fracture classification, and new fractures. These factors probably combine and result in a high pain score after 12 months (23). Therefore, PV may be useful when fracture healing is incomplete.

No association between use of polymethylmethacrylate and development of new fractures at adjacent or remote levels was observed, which is in accordance with the VERTOS II and IV results. This suggests that these fractures are the natural history of the osteoporotic disease and not related

to cementation. We observed no vertebral height loss in the active control group versus the PV group. However, in the conservative therapy group of VERTOS II and the noncement group of VERTOS IV, this difference compared with the PV group was significant (8,14). Progressive vertebral collapse occurs in noncemented vertebrae and may lead to compression of the spinal cord, as seen once in this study and twice in VAPOUR (9). Thus, conservative therapy does not imply risk-free therapy (24,25). Moreover, the U.S. Medicare data set found a significant adjusted survival benefit for patients who underwent PV compared with conservative management (26).

The strength of this trial is that nearly all participants (94%) were convinced they received the actual cementation, with no crossovers. In other words, the placebo effect (expectations of pain relief) was high, but nevertheless, PV was significantly better than active control (placebo) for pain and health-related quality of life.

We acknowledge several study limitations. First, in line with previous methodologic criticisms about the VERTOS IV design, VERTOS V also used an "active control" of lidocaine and bupivacaine. Our objective was not to compare the effects of PV versus active control, but rather to compare the effects of cementation versus no cementation. Second, our sample size of 80 participants allowed detecting a difference of three points on the 10-point VAS scale with a power of 0.80, suggesting that our study was not sufficiently powered to detect the smaller differences observed in our study, including the minimum clinically important VAS difference of 1.5 (27). Third, though statistically significant, the difference between the PV and active control groups in reduced pain was slightly smaller than the predefined threshold of clinical significance. Finally, our results only relate to chronic (>3 months) painful OVCFs.

Compared with active control, percutaneous vertebroplasty (PV) intervention led to pain reduction and better health-related quality of life in participants with chronic osteoporotic vertebral compression fracture. We believe that future research should focus on PV versus true sham intervention in a multicenter trial with at least 1 year of follow-up.

Author contributions: Guarantors of integrity of entire study, **D.C., K.S., A.S., J.d.V., P. Lohle**; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, **A.V., I.B., K.S., A.S., J.H., P. Lohle**; clinical studies, **D.C., A.V., E.D., K.S., A.S., C.S., J.d.V., P. Lohle**; experimental studies, **K.S., A.S.**; statistical analysis, **A.V., P. Lodder, T.v.O., K.S., A.S., J.d.V., P. Lohle**; and manuscript editing, **A.V., P. Lodder, T.v.O., K.S., A.S., J.H., P. Lohle**

Data sharing: All data generated or analyzed during the study are included in the published paper.

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