Investigational Vertebroplasty Safety and Efficacy Trial (INVEST): Patient-reported Outcomes through 1 Year¹

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Purpose:

To evaluate 1-year outcomes of the Investigational Vertebroplasty Safety and Efficacy Trial (INVEST), a blinded, randomized, controlled trial to investigate the effectiveness of percutaneous vertebroplasty in the treatment of osteoporotic vertebral compression fractures.

Materials and Methods:

Patients were enrolled at 11 sites in the United States, the United Kingdom, and Australia by using an institutional review board–approved protocol and HIPAA compliance, and all patients provided written informed consent. Patients were randomized to undergo vertebroplasty or a control procedure. After 1 month, patients were allowed to cross over and undergo the alternate procedure. Coprimary outcomes were patient-reported function, measured with the modified Roland-Morris Disability Questionnaire (RDQ), and pain (on a scale of one to 10) at 1 year. Intention-to-treat (ITT) and as-treated (AT) analyses were used to compare outcomes.

Results:

One hundred thirty-one participants (68 in the vertebroplasty group and 63 in the control group) were included in the analyses. Patients in both groups showed improvements in pain and function at 1 year. In ITT analyses, patients randomized to vertebroplasty did not differ from control subjects in terms of RDQ results (difference, 1.37 points; 95% confidence interval [CI]: −0.88, 3.62; $P = .231$) but reported lower levels of pain (difference, 1.02 points; 95% CI: 0.04, 2.01; $P = .042$). Eleven of 68 patients who underwent vertebroplasty (16%) and 38 of 63 control subjects (60%) crossed over and elected to undergo the alternate procedure ($P < .001$). In AT analyses, patients treated with vertebroplasty did not differ from control subjects in terms of RDQ results (difference, 0.66 points; 95% CI: −1.98, 3.30; $P = .625$) or pain (difference, 0.85 points; 95% CI: −0.35, 2.05; $P = .166$).

Conclusion:

Vertebroplasty may provide a modest reduction in pain at 1 year compared with a control procedure; however, no difference in functional disability was observed.

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Spontaneous, painful vertebral fractures represent an important cause of morbidity and mortality among patients with osteoporosis. Percutaneous vertebroplasty—the injection of medical cement, or polymethylmethacrylate (PMMA) (Parallax Medical, Wilmington, Mass), into the fractured vertebral body—has gained widespread acceptance as a method of pain relief and is a part of routine therapy for osteoporotic vertebral fractures (1).

We previously reported primary outcomes data through 1 month of the Investigational Vertebroplasty Safety and Efficacy Trial (INVEST) (2). INVEST was designed as a double-blinded, randomized controlled trial (RCT) to evaluate the effectiveness of PMMA infusion for patients with painful, osteoporotic compression fractures, as compared with a simulated vertebroplasty conducted without the use of PMMA. The primary hypothesis of the trial was that patients assigned to vertebroplasty, as compared with those assigned to the control procedure, would report less pain and back pain–related disability at 1 month. The INVEST study findings demonstrated that patients treated with vertebroplasty showed no significant differences in pain or functional disability at 1 month, compared with those treated with the control procedure (2).

Advances in Knowledge

- Patient ratings of pain after 1 year among those randomized to vertebroplasty were significantly better than those of subjects randomized to a control procedure (mean difference, 1.02 points; 95% confidence interval [CI]: 0.04, 2.01; $P = .042$), but the severity of patient-reported functional disability was similar between groups (mean difference, 1.37 points; 95% CI: −0.88, 3.62; $P = .231$).
- The placebo effect, blinding, and patient expectation may have heavily influenced the reported 1-year outcomes of patients treated with vertebroplasty.

INVEST was one of two blinded RCTs that showed little to no differential benefit of vertebroplasty relative to a control procedure in short-term patient-reported outcomes (2,3). We now report on the primary outcomes measured through 1 year after randomization among INVEST participants.

Materials and Methods

Study Design and Implementation

Between June 2004 and August 2008, we enrolled patients in a Health Insurance Portability and Accountability Act–compliant, institutional review board–approved, blinded, parallel-group RCT at five sites in the United States, five sites in the United Kingdom, and one site in Australia. The study protocol was developed by experts in the fields of radiology (D.F.K. and J.G.J., with 17 and 25 years of experience, respectively), psychiatry (J.A.T., with 35 years of experience), and biostatistics (P.J.H., with 20 years of experience) and was approved by the local institutional review board at each recruitment site. All study participants provided written informed consent. The study methods and 1-month outcome measures have been described in detail elsewhere (2). Patients were eligible for the study if they were 50 years or older, had a diagnosis of one to three painful osteoporotic vertebral compression fractures between vertebral levels T4 and L5, had inadequate pain relief with standard medical therapy, and rated their pain intensity with a score of at least 3 on a scale from zero to 10. Fractures were required to be less

than 1 year old, as indicated by patient-reported duration of pain. Exclusion criteria were evidence or suspicion for neoplasm in the target vertebral body, substantial retropulsion of bony fragments, concomitant hip fracture, active infection, uncorrectable bleeding diathesis, surgery within the previous 60 days, lack of access to a telephone, inability to communicate in English, and dementia.

Treatment

As described previously, patients were initially randomized to the full vertebroplasty procedure or to a control intervention (2). For all patients in the study, the skin and subcutaneous tissues overlying the pedicle of the target vertebra or vertebrae were infiltrated with 1% lidocaine, and the periosteum of the pedicles was infiltrated with 0.25% bupivacaine by using fluoroscopic guidance. For the control intervention, verbal and physical cues, such as pressure on the patient's back, were given, and the container of

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Abbreviations:

AT = as treated

CI = confidence interval

INVEST = Investigational Vertebroplasty Safety and Efficacy Trial

ITT = intention to treat

PMMA = polymethylmethacrylate

RCT = randomized controlled trial

RDQ = Roland-Morris Disability Questionnaire

VERTOS = Vertebroplasty versus Conservative Treatment in Acute Osteoporotic Vertebral Compression Fractures

Author contributions:

Guarantor of integrity of entire study, B.A.C.; 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; literature research, B.A.C., J.G.J., J.A.T., D.F.K.; clinical studies, J.G.J., J.A.T., D.F.K.; statistical analysis, B.A.C., C.M.S., P.J.H.; and manuscript editing, all authors

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

Implication for Patient Care

- With a modest benefit toward pain and no benefit toward functional disability at 1 year, the role of vertebroplasty in the treatment of painful vertebral compression fractures warrants further study; future blinded, randomized, controlled trials may help identify subgroups of patients for whom the procedure is both safe and effective.

methacrylate monomer was opened to simulate the odor associated with the mixing of PMMA, but the needle was not placed, and PMMA was not infused. For each recruitment site, randomized treatment assignments were generated by the data-coordinating center and sealed in numbered, opaque envelopes. Randomization envelopes were opened immediately prior to the procedure, and all patients underwent the randomly assigned treatment according to the protocol for that procedure. We attempted to mask all patients and study personnel who performed follow-up assessments in regard to treatment assignments for the duration of the study. Only the treating physician in each procedure knew which treatment was being given, and only the study statistician (who did not have any contact with study participants) had access to unblinded patient-reported outcomes data.

Patients were told at the time of consent that they would be allowed to cross over and undergo the alternative procedure at 1 month or later after the initial intervention if adequate pain relief was not achieved. A specific numerical threshold of pain relief was not used for allowance of crossover. Patients met with a vertebroplasty practitioner in the clinic 1 month after the initial procedure to discuss whether the patient should cross over and receive the alternative therapy. A crossover script was used at each site in an attempt to standardize part of the crossover discussion between the patient and practitioner, although patient-reported reasons for choosing to cross over were not recorded. In addition, when feasible, a second vertebroplasty practitioner, who was blinded to the initial treatment assignment, discussed crossover with the patient at the 1-month visit. However, a second blinded practitioner was not always available at each recruitment site.

Measures

Prior to randomization, patients provided demographic and clinical information and filled out a battery of questionnaires to evaluate functional status, pain, and quality of life. At 14 days, patients were asked to rate their perception of treatment received by providing a guess

about which procedure they had undergone, along with a rating of confidence in their guess. Outcome measures were repeated at fixed times of 1, 3, and 6 months and 1 year after randomization. The focus of this report is on outcomes measured at 1 year.

The prespecified primary outcome measures were the modified Roland-Morris Disability Questionnaire (RDQ) (4) and a numerical rating of back pain intensity measured at the 1-month visit, and here we report on RDQ results and pain through 12 months. The 23-item RDQ is widely used to assess physical disability associated with back pain and has been shown to be valid, reliable, and responsive to change (5). Patients rated their average back-pain intensity during the preceding 24 hours on a scale of zero (no pain) to 10 (pain as bad as it could be). In keeping with recommended guidelines for reporting in trials related to chronic pain, we also calculated the number of patients who had a 30% or greater improvement in pain from baseline to 12 months (6).

Sample Size

The study was initially powered to detect differences in primary and secondary outcomes measured at 1 month (initial study group, 250 participants; $\alpha = .05$; power > 80%). With the approval of an independent data and safety monitoring board, the target sample size was reduced to 130 randomized participants to maintain the power (> 80%) to detect important differences in the primary outcome measures: a 3.0-point difference between groups according to the RDQ findings and a 1.5-point difference on the pain rating scale. Smaller group differences with each measure were not considered to be clinically meaningful. Group sequential stopping boundaries were used to monitor 1-month outcome measures for effectiveness (final significance level, $P < .043$) but were not reached during the study.

Statistical Analysis

For the primary analyses of outcomes through 12 months, we used an intention-to-treat (ITT) strategy, with

patients analyzed according to their randomly assigned group. Treatment effects and confidence intervals (CIs) were calculated from analysis of covariance models, adjusting for baseline values of the outcome measure and recruitment site and using a treatment indicator as the predictor of interest. ITT comparisons of the proportion of patients reporting a 30% or greater improvement in pain were evaluated similarly but with a logistic regression model.

Because patients were allowed the option to cross over and receive the alternate treatment, 1-year ITT estimates of treatment effect include a mixture of patients who adhered to the original treatment assignment and those who underwent both procedures. We therefore also used two separate as-treated (AT) strategies to evaluate the effect of vertebroplasty, on the basis of the treatment received.

In the first AT analysis, we grouped patients according to whether they underwent vertebroplasty at any time during the study, either by being randomized to vertebroplasty initially or by crossing over from the control arm. We calculated treatment effects and CIs from analysis of covariance models of RDQ results and pain ratings, with an indicator of vertebroplasty as the predictor of interest. This simple AT strategy, which is descriptive and mimics an observational study design, is probably biased because of differential crossover patterns between randomized groups and biases inherent with treatment self-selection.

We implemented a second AT strategy to more appropriately account for the time-varying nature of subsequent vertebroplasty procedures. We created a time-varying indicator of whether patients underwent vertebroplasty by a given outcome assessment time. Treatment effects and CIs were calculated by using linear mixed-effects models with random intercepts and slopes, with a time-varying treatment indicator as the predictor of interest (7). The number of days that had elapsed between vertebroplasty and the time of outcome assessment was also included in the model to allow an immediate effect of

vertebroplasty, plus an additional effect over time after the procedure (8).

In each AT analysis, we adjusted for baseline values of both primary outcome measures (RDQ results and pain intensity). We used univariate logistic regression models to evaluate and identify pretreatment demographic factors, clinical characteristics, and measures of outcome that were associated with patient crossover. Pretreatment variables that could be used to predict crossover ($P < .05$), independently of the randomized treatment assignment or differentially by treatment assignment, were adjusted for in both AT analyses. Posttreatment outcomes and treatment guesses at 14 days were similarly examined for associations with crossover.

All reported treatment effects are coded such that positive numbers favor vertebroplasty, and all P values are two sided and not adjusted for interim monitoring or multiple testing. Study statisticians (P.J.H., B.A.C., and C.M.S., with 20, 11, and 8 years of experience, respectively) were responsible for statistical design considerations and analyses, which were performed by using R statistical software (version 2.10; R Foundation, Vienna, Austria) (9).

Results

Between June 2004 and August 2008, 131 patients were enrolled and randomized (Fig 1). Sixty-eight patients were randomized to vertebroplasty and 63 to the control intervention; all underwent the assigned intervention. Sixty-three of 68 patients (93%) in the vertebroplasty group and 56 of 63 subjects (89%) in the control group completed the 1-year assessment. Two patients (3%) in the vertebroplasty group and three subjects (5%) in the control group died during the study period; all but one of these five died after 6 months of follow-up, and no deaths were known to be study related. In the year after randomization, 11 of 68 patients (16%) in the vertebroplasty group and 38 of 63 patients (60%) in the control group crossed over ($P < .001$). This crossover mostly occurred between 1 and 3 months after randomization.

Although patient-reported reasons for crossover were not recorded as a part of the study protocol, in Table 1 we present pre- and posttreatment factors and univariate odds ratios for crossover. Study recruitment site, duration of pain, marital status, and self-reported opioid medication use were pretreatment factors associated with crossover, regardless of treatment group assignment. Posttreatment factors associated with crossover included the 14-day values of RDQ measurements and pain intensity. Patients with higher levels of functional disability or pain were more likely to cross over (RDQ results, $P = .002$; pain,

$P < .001$). Similarly, patients who experienced greater 14-day change in functional disability or pain were less likely to cross over in either treatment group (RDQ results and pain, $P < .001$). Patients in both treatment groups who guessed at 14 days that they had undergone the control procedure were nearly three times more likely to cross over, compared with patients who guessed that they had undergone vertebroplasty (vertebroplasty group odds ratio, 2.95; 95% CI: 0.99, 8.79; control group odds ratio, 2.84; 95% CI: 0.66, 12.24).

In ITT analyses of 1-year outcomes, patients randomized to vertebroplasty

Figure 1

Figure 1: Flowchart shows treatment and follow-up of study participants. Assessment was considered to be complete at a given time if both primary outcome measures were collected. Data are cumulative, with the exception of total crossover.

Table 1

Odds of Crossing Over in Each Group according to Baseline Demographics, Clinical Characteristics, and Outcome Measures

Characteristic	Odds Ratio		P Value*	
	Vertebroplasty	Control Procedure	Overall	Differential
Study recruitment site				
Mayo Clinic (<i>n</i> = 30)	Reference	Reference	.01	.49
Oxford, UK (<i>n</i> = 52)	2.2 (0.4, 12.5)	3.5 (0.9, 12.9)		
Australia (<i>n</i> = 22)	5.2 (NC)	0.6 (0.1, 3.5)		
Other U.S. or UK sites (<i>n</i> = 27)	0.9 (0.1, 7.6)	3.9 (0.7, 19.8)		
Demographics				
Age†	0.99 (0.93, 1.06)	0.97 (0.92, 1.02)	.30	.57
Women (<i>n</i> = 99)	0.7 (0.2, 3.1)	0.8 (0.2, 2.5)	.54	.93
Less than high-school education (<i>n</i> = 62)	0.7 (0.2, 2.6)	0.6 (0.2, 1.8)	.30	.90
Married or living with another person (<i>n</i> = 69)	3.5 (0.7, 17.7)	2.9 (1.0, 8.4)	.01	.83
Retired (<i>n</i> = 81)	0.7 (0.2, 2.6)	1.5 (0.5, 4.3)	.78	.37
Clinical characteristics				
Pain duration				
1–13 weeks (<i>n</i> = 54)	Reference	Reference	.01	.45
14–26 weeks (<i>n</i> = 29)	1.5 (0.2, 10.2)	6.7 (1.5, 30.2)		
27–52 weeks (<i>n</i> = 48)	3.0 (0.7, 13.6)	4.0 (1.2, 13.5)		
Self-reported opioid medication use (<i>n</i> = 78)	2.4 (0.6, 9.9)	2.3 (0.8, 6.5)	.05	.95
More than one fracture (<i>n</i> = 42)	0.9 (0.2, 3.7)	0.7 (0.2, 2.0)	.51	.79
Pretreatment outcome measures				
RDQ results	0.99 (0.83, 1.17)	1.00 (0.89, 1.14)	.97	.87
Average pain intensity	1.04 (0.74, 1.45)	1.04 (0.79, 1.37)	.72	.99
Posttreatment outcome measures				
RDQ results				
At 14 days	1.19 (1.01, 1.38)	1.10 (1.00, 1.21)	.002	.40
14-day change from baseline	0.81 (0.67, 0.97)	0.88 (0.79, 0.99)	<.001	.40
Average pain intensity				
At 14 days	1.43 (1.09, 1.88)	1.38 (1.11, 1.72)	<.001	.84
14-day change from baseline	0.69 (0.52, 0.92)	0.80 (0.67, 0.96)	<.001	.40
Guessed control procedure at 14 days	2.84 (0.66, 12.24)	2.95 (0.99, 8.79)	.01	.97

Note.—Numbers in parentheses are 95% CIs. NC = not calculable, reference = reference category in the logistic regression model.

* Overall *P* values were calculated with separate univariate logistic regression models, where each characteristic was evaluated as a predictor of crossover, independent of randomized group assignment. To determine whether characteristics were more predictive of crossover in one treatment group over the other, differential *P* values were calculated by including an interaction term between each characteristic and randomized group assignment in the logistic regression model.

† Mean age ± standard deviation, 73.8 years ± 9.5.

did not differ significantly from those in the control group in terms of RDQ findings (mean difference, 1.37; 95% CI: −0.88, 3.62; *P* = .231) but did report modestly lower pain intensity (mean difference, 1.02; 95% CI: 0.04, 2.01; *P* = .042) (Table 2). Forty-four of 63 patients (70%) randomized to vertebroplasty and 25 of 56 (45%) randomized to the control group showed a 30% or greater improvement in pain at 1 year (*P* = .004).

In Figure 2, mean RDQ scores and pain intensity are grouped and plotted according to adherence to treatment. In the simple AT analyses, those treated

with vertebroplasty at any time during the study did not differ significantly from those who were not treated with vertebroplasty in terms of either RDQ findings (adjusted mean difference, −2.20; 95% CI: −4.98, 0.58; *P* = .119) or pain intensity (adjusted mean difference, −0.55; 95% CI: −1.83, 0.73; *P* = .397) at 1 year. Furthermore, in the robust AT analyses in which mixed-effects models were used (Fig 2), no significant differences at 1 year were observed for either the RDQ results (adjusted mean difference, 0.66; 95% CI: −1.98, 3.30; *P* = .625) or pain intensity (adjusted

mean difference, 0.85; 95% CI: −0.35, 2.05; *P* = .166).

Discussion

One year after being randomized to undergo either vertebroplasty or a control procedure, patients in both groups showed significant improvement in functional disability and pain outcomes. In ITT analyses, where outcomes were analyzed according to randomized group, we found no evidence for a difference between groups in functional disability outcomes at 1 year. However, patients ran-

Table 2

ITT Treatment Comparison of Primary Outcome Measures

Primary Outcome Measures	Vertebroplasty		Control Procedure		Treatment Comparison*	P Value*
	Mean	Mean Change from Baseline	Mean	Mean Change from Baseline		
RDQ score [†]						
Baseline	16.62 ± 3.80	...	17.52 ± 4.14	...	...	
1 Month	11.97 ± 6.32	−4.64 ± 6.25	12.97 ± 6.38	−4.52 ± 5.89	0.73 (−1.33, 2.79)	.486
3 Months	10.84 ± 5.68	−5.86 ± 5.40	11.89 ± 6.37	−5.69 ± 5.67	0.75 (−1.15, 2.64)	.437
6 Months	9.44 ± 6.12	−7.19 ± 6.03	11.38 ± 6.35	−6.26 ± 6.58	1.64 (−0.51, 3.78)	.134
12 Months	10.19 ± 6.46	−6.37 ± 6.46	11.89 ± 6.24	−5.62 ± 6.45	1.37 (−0.88, 3.62)	.231
Average pain intensity [‡]						
Baseline	6.88 ± 1.96	...	7.16 ± 1.84	...	...	
1 Month	3.85 ± 2.91	−3.01 ± 3.18	4.57 ± 2.97	−2.56 ± 3.11	0.68 (−0.34, 1.69)	.192
3 Months	3.55 ± 2.81	−3.31 ± 3.00	4.26 ± 2.85	−2.85 ± 2.97	0.74 (−0.23, 1.70)	.133
6 Months	3.67 ± 2.98	−3.25 ± 3.03	4.43 ± 2.89	−2.66 ± 3.25	0.80 (−0.22, 1.82)	.125
12 Months	3.52 ± 2.89	−3.44 ± 3.29	4.50 ± 2.70	−2.54 ± 2.95	1.02 (0.04, 2.01)	.042

Note.—Data are means ± standard deviations, unless specified otherwise. Numbers in parentheses are 95% CIs.

* Treatment comparisons, 95% CIs, and P values are calculated from analysis of covariance models that adjust for randomized treatment assignment, the baseline value of the outcome measure, and recruitment site. Negative treatment effects favor the control procedure, and positive treatment effects favor vertebroplasty.

[†] The RDQ is scored from 0 to 23, with 23 representing the worst functioning.

[‡] Average pain intensity in the preceding 24 hours, scored from 0 (no pain) to 10 (pain as bad as it can be).

domized to undergo vertebroplasty reported significantly less pain at 1 year than did those randomized to the control procedure. In robust AT analyses, where data were analyzed according to treatment actually received over the course of the study, functional disability and pain outcomes at 1 year were not found to differ significantly according to treatment.

Crossover rates in our study differed between treatment groups, with patients initially assigned to the control procedure crossing over significantly more often than those assigned to vertebroplasty. Crossover mostly occurred between 1 and 3 months after randomization in both groups. The fact that 60% of control subjects had actually undergone vertebroplasty by crossing over complicates the interpretation of the ITT analyses of 1-year outcomes. Specifically, if vertebroplasty is in fact more effective than the control procedure, then one would expect to observe a diluted treatment effect, or no difference, in ITT analyses. However, subjects in the control group who subsequently crossed over and underwent vertebroplasty clearly did not experience similar outcomes to those initially randomized to vertebroplasty.

All AT groups showed dramatic improvement in functional disability not only from baseline to 1 month, but also from 1 month to 3 months. After 3 months, however, patient-reported functional disability and pain did not improve after crossing over in either group. Control subjects who did not cross over showed an even greater improvement than did the patients who were assigned to vertebroplasty and did not cross over from 1 month to 3 months. While our study does not allow us to definitively identify reasons for these observations, it is likely that some combination of placebo effects and natural history may result in continued improvement in disability through 3 months. It also remains possible that the good long-term outcomes observed among patients who adhered to initial treatment are indicative of an unexplained “responder” cohort, relative to patients who crossed over.

Crossover, a tool to enhance study enrollment, was not a defined outcome of the study, yet it appears to be associated with poor functional and pain outcomes both at the time of the decision to cross over and long term. We cannot explain the reasons for differential

crossover between groups, although recruitment site, a guess at 14 days that the participant was randomized to the control condition, less improvement in 14-day changes, and higher levels of disability (RDQ scores) and pain were among the factors that contributed to prediction of crossover, regardless of initial group assignment.

Other previous RCTs of augmentation for vertebral compression fractures differ substantially from the current study in design and implementation (3,10–13). The blinded RCT of Buchbinder et al (3) did not allow crossover and therefore provides long-term comparisons for a different clinical treatment protocol. One RCT conducted by the Vertebroplasty versus Conservative Treatment in Acute Osteoporotic Vertebral Compression Fractures (VERTOS) research group showed moderate pain relief among patients who underwent vertebroplasty compared with an unmasked conservative treatment control group at both 1 month and 1 year (10,11). More recently, the VERTOS research group reported that a blinded randomized sham-controlled trial of vertebroplasty was under way (12). The

Figure 2

Figure 2: Graphs show mean RDQ scores (top) and average pain intensity scores (bottom), with 95% CIs, according to treatment adherence over time. AT vertebroplasty effect estimates and 95% CIs were obtained by using mixed-effects models with random intercepts and a time-varying indicator of when treatment was received. Treatment effects are coded such that negative treatment effects favor the control procedure and positive treatment effects favor vertebroplasty.

current VERTOS IV study has a design similar to the INVEST and Australian studies, demonstrating that the medical treatment question remains as to whether the injection of PMMA is an effective treatment or whether longitudinally observed improvement in outcomes may be the result of a natural improvement subsequent to care-seeking episodes or simply a placebo effect.

The high rate of patient crossover from the control group to vertebroplasty

was a limitation and challenge in evaluating patient-reported outcomes at 1 year in the present study. With the guidance of their treating physician, patients decided whether or not to cross over and undergo the alternate procedure. While a crossover script was provided to all study recruitment sites, adherence to the crossover script was not measured systematically in the study. We speculate, but cannot definitively prove, that treating physicians in the study may have

been more likely to advise crossover to patients initially randomized to the control procedure than to those randomized to vertebroplasty. It will be important in future studies for treating physicians to be blinded to interventions performed.

Another limitation was that the study was not adequately powered to identify subgroups of patients for whom vertebroplasty may be beneficial relative to the control procedure. At 1 year, 23 of 63 patients (36%) randomized to the control group and 53 of 68 (78%) randomized to vertebroplasty adhered to the initial treatment assignment, and both groups on average had better functional and pain outcomes relative to those who crossed over. This leaves open the possibility that certain subgroups of patients may benefit more from one treatment than the other. Finally, we specifically enrolled patients with painful osteoporotic fractures and asked them to rate their average back pain with a numerical rating scale. Pain generators other than the initial compression fracture may have influenced the follow-up pain response, although this would have affected both groups.

Given the observed short- and long-term outcomes of this study, the role of vertebroplasty in the treatment of painful vertebral compression fractures warrants further study. It remains possible that future, blinded RCTs, such as VERTOS IV, may help identify patient subgroups that achieve benefit from the procedure.

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