

Safety and efficacy of vertebroplasty for acute painful osteoporotic fractures (VAPOUR): a multicentre, randomised, double-blind, placebo-controlled trial



William Clark, Paul Bird, Peter Gonski, Terrence H Diamond, Peter Smerdely, H Patrick McNeil, Glen Schlaphoff, Carl Bryant, Elizabeth Barnes, Val Gebski

Summary

Background We hypothesised that vertebroplasty provides effective analgesia for patients with poorly controlled pain and osteoporotic spinal fractures of less than 6 weeks' duration. The effectiveness of vertebroplasty, using an adequate vertebral fill technique, in fractures of less than 6 weeks' duration has not been specifically assessed by previously published masked trials.

Methods This was a multicentre, randomised, double-blind, placebo-controlled trial of vertebroplasty in four hospitals in Sydney, Australia. We recruited patients with one or two osteoporotic vertebral fractures of less than 6 weeks' duration and Numeric Rated Scale (NRS) back pain greater than or equal to 7 out of 10. We used an automated telephone randomisation service provided by the National Health and Medical Research Council to assign patients (1:1; stratified according to age, degree of vertebral compression, trauma, corticosteroid use, and hospital) to either vertebroplasty or placebo, immediately before the procedure. Patients received conscious sedation. Vertebroplasty was done with the adequate vertebral fill technique and the placebo procedure with simulated vertebroplasty. Follow-up was for 6 months. Outcome assessors and patients were masked to treatment allocation. The primary outcome was the proportion of patients with NRS pain below 4 out of 10 at 14 days post-intervention in the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT01482793.

Findings Between Nov 4, 2011, and Dec 5, 2014, 120 patients were enrolled. 61 patients were randomly assigned to vertebroplasty and 59 to placebo. 24 (44%) patients in the vertebroplasty group and 12 (21%) in the control group had an NRS pain score below 4 out of 10 at 14 days (between-group difference 23 percentage points, 95% CI 6–39; $p=0.011$). Three patients in each group died from causes judged unrelated to the procedure. There were two serious adverse events in each group, related to the procedure (vertebroplasty group) and the fracture (control group).

Interpretation Vertebroplasty is superior to placebo intervention for pain reduction in patients with acute osteoporotic spinal fractures of less than 6 weeks' in duration. These findings will allow patients with acute painful fractures to have an additional means of pain management that is known to be effective.

Funding Education grant from CareFusion Corporation.

Introduction

Osteoporotic vertebral fractures affect an estimated 1.4 million patients in the world annually.¹ Although most have mild symptoms, a subset of patients develop substantial pain and disability and some require admission to hospital.² Standard therapy, consisting of rest, analgesia, and mobilisation, is often poorly tolerated in elderly people, with the adverse effects of analgesia and immobilisation leading to additional health problems, including poor cognition, increased risk of falls, constipation, and nausea.³

Vertebroplasty, the injection of polymethylmethacrylate (PMMA) into the fractured vertebral body, is frequently used for symptomatic osteoporotic fractures, and is based on the premise that fracture stabilisation can provide pain relief. Optimum timing for vertebroplasty is controversial. Because symptoms from painful vertebral fractures might improve over time, a common approach has been to allow the fracture to heal, a process spanning up to 12 months, and intervene only in patients with

persistent pain. Two masked randomised controlled trials (RCTs)^{4,5} have investigated this approach and found no significant benefit of vertebroplasty in patients with osteoporotic fractures of up to 12 months in duration when compared with a placebo. Early intervention was not assessed as a primary outcome in these trials, and the volume of cement used per patient was small, raising the question of whether vertebral stability was achieved.⁶

We hypothesise that vertebroplasty can effectively reduce pain if done with an adequate vertebral fill technique within 6 weeks of fracture onset. Evidence from open-label RCTs^{7–9} supports the premise of early intervention. However, evidence is deficient from the two masked trials¹⁰ because less than 25% (25 of 106) of vertebroplasty patients in pooled data had fractures of less than 6 weeks' duration.

To understand better the safety and effectiveness of vertebroplasty for patients with painful fractures of less than 6 weeks' duration, we undertook a study masked to patients and assessors comparing vertebroplasty with a

Published Online
August 17, 2016
[http://dx.doi.org/10.1016/S0140-6736\(16\)31341-1](http://dx.doi.org/10.1016/S0140-6736(16)31341-1)

This online publication has been corrected. The corrected version first appeared at thelancet.com on August 23, 2016

See Online/Comment
[http://dx.doi.org/10.1016/S0140-6736\(16\)31356-3](http://dx.doi.org/10.1016/S0140-6736(16)31356-3)

St George and Sutherland Clinical School (P Bird PhD, T H Diamond MD), School of Public Health & Community Medicine (P Gonski MD, P Smerdely PhD), and South Western Sydney Clinical School (G Schlaphoff MD), University of New South Wales, Sydney, NSW, Australia; Department of Aged Care, Sutherland Hospital, Caringbah, NSW, Australia (P Gonski); Department of Endocrinology (T H Diamond) and Department of Aged Care (P Smerdely), St George Hospital, Kogarah, NSW, Australia; Faculty of Medicine and Health Sciences, Macquarie University, Sydney, NSW, Australia (Prof H P McNeil PhD); Department of Interventional Radiology, Liverpool Hospital, Liverpool, NSW, Australia (G Schlaphoff); Department of Radiology, St George Private Hospital, Kogarah, NSW, Australia (W Clark MD, C Bryant MD); and NHMRC Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia (E Barnes MStat, Prof V Gebski MStat)

Correspondence to: Dr William Clark, Department of Interventional Radiology, St George Private Hospital, Kogarah, NSW, Australia williamxrayclark@bigpond.com

Research in context

Evidence before this study

A systematic literature review by the Australian Medicare Services Advisory Committee in 2011 focused on three good quality randomised trials of vertebroplasty. Two masked trials (Kallmes and colleagues, Buchbinder and colleagues) enrolled patients with fractures up to 12 months' duration and found vertebroplasty no more effective than placebo in pain reduction. Subgroup meta-analysis of these masked trials (by Staples and colleagues) identified 57 patients with fractures of less than 6 weeks' duration, and found vertebroplasty no more effective than placebo in this acute fracture subgroup. Conversely, an open-label randomised trial (Klazen and colleagues) of patients with fractures of less than 6 weeks' duration showed that vertebroplasty was more effective than conservative care in reducing pain. The review concluded that the two masked trials were of superior methodological quality and provided evidence of lack of efficacy for vertebroplasty. However, the small representation of patients with uncontrolled pain and acute fractures of less than 6 weeks' duration in the masked trials caused uncertainty for the role of vertebroplasty in this subgroup. The review recommended a high quality placebo-controlled trial to specifically assess this patient group. This is such a trial.

Added value of this study

This randomised, parallel group, placebo-controlled trial, was designed to answer the question as to whether vertebroplasty compared with placebo improved pain measures, primarily, and disability measures, secondarily, in patients with fractures of less than 6 weeks' duration. There were 120 patients, twice the number of the subgroup meta-analysis of previous masked trials, thereby increasing the statistical power. Our findings show that vertebroplasty improved both pain and disability measures.

Implications of all the available evidence

Until now, there has been no evidence that vertebroplasty was more effective than placebo in the treatment of acute, painful, osteoporotic vertebral fractures, most notably for those in the thoracolumbar region. No masked studies have exclusively examined acute fractures of less than 6 weeks' duration but only in a subgroup analysis with small patient numbers. Our study will allow those people with acute painful fractures to have an additional modality of pain management that is known to be effective.

placebo procedure—the Vertebroplasty for Acute Painful Osteoporotic fractures (VAPOUR) trial.

Methods

Study design and participants

This randomised, parallel group, placebo-controlled trial of vertebroplasty was done in four centres in Sydney, Australia. There was a 6-month follow-up period. The protocol, reported previously,¹¹ is a modification of the protocol from the INVEST trial⁴ in which two of our authors were investigators.

Participants were referred to interventional radiology from primary care practitioners, medical specialists' consulting rooms, and hospital inpatient and emergency departments. The patient was screened for eligibility, advised of the trial process, and given a detailed patient information document to consider. If the patient consented to participate, an outcome assessor arranged an interview, rechecked eligibility criteria, recorded baseline data, and arranged follow-up interviews.

Inclusion criteria were patients older than 60 years, with back pain of less than 6 weeks' duration, a Numeric Rated Scale (NRS) pain score of 7 or more (out of 10), and an MRI confirming one or two recent fractures. If an MRI was contraindicated, single-photon emission computed tomography–computed tomography was done. Exclusion criteria were inability to provide informed consent, chronic back pain requiring opiate use, substantial fracture retropulsion, acute infection, spinal malignancy, neurological complications, and greater than two vertebral fractures. The four participating vertebroplasty procedure centres in Sydney, Australia, had established

vertebroplasty practices. All interventional radiologists had undergone vertebroplasty training and were actively providing a vertebroplasty service.

The trial was approved by the Human Research Ethics Committees of Bellberry Limited (2011-08-414) and North Sydney Local Health District (HREC/11/HAWKE/228). The Human Research Committee at each participating centre approved the study and all patients provided written informed consent. An independent safety committee consisting of two physicians reviewed serious adverse events during the trial as they were reported and then every 6 months.

Randomisation and masking

Participants were randomly assigned (1:1) to receive either vertebroplasty or placebo by the National Health and Medical Research Council (NHMRC) Clinical Trials Centre automated telephone service, which provided random computer-generated numbers. The interventional radiologist called this system once the patient was in the procedure room, immediately before the procedure. Randomisation was stratified according to age, vertebral height loss, trauma, steroid use, and intervention centre. The participants, investigators (other than radiologists doing the procedure), and trial outcome assessors were masked to patient group assignments. To enhance masking, neither the radiologist nor staff at the treating centres had any other role in the trial.

Procedures

The participant was positioned prone on the procedure table with oxygen mask applied. Pulse oximetry and rate were monitored continuously. Intravenous midazolam and fentanyl were given to all patients before starting the

procedure. Lidocaine was injected subcutaneously and a 4 mm skin incision was made.

For vertebroplasty, an 11-gauge or 13-gauge vertebroplasty needle was introduced into the vertebral body with either a unipedicular or bipedicular technique with fluoroscopic guidance. We used an AVAMAX kit (CareFusion Corporation) according to the approved kit technique. The aim was to fill the vertebral body with sufficient PMMA to prevent future collapse—from superior to inferior endplate, mid-pedicle to mid-pedicle in frontal projection, and from anterior cortex to posterior third of vertebral body. Injection was ceased when these endpoints were reached or if PMMA extravasated outside the bone. PMMA volume and extravasation were recorded.

The placebo procedure, designed to simulate vertebroplasty, included subcutaneous lidocaine but not periosteal numbing. A short needle was passed into the skin incision but not as far as the periosteum. Manual skin pressure and regular tapping on the needle was done, mimicking vertebroplasty needle advance. Conversation about PMMA mixing and injection suggested that vertebroplasty was being done. After the procedure, participants received the usual medical care directed by their attending physicians.

Data were obtained at baseline, 3 days, 14 days, and 1, 3, and 6 months after the procedure. Baseline, 14 day, and 6 month interviews were done in person by research staff. The remaining interviews (day 3, month 1, and month 3) were done by telephone by the same, masked research staff. Patients unable to visit the research office at day 14 and 6 months were interviewed by telephone.

Outcomes

The primary outcome measure was the NRS pain score at 14 days after the intervention. The NRS measured pain over the previous 24 h, on a scale of 0–10 (0 indicating no pain and 10 maximum pain). The primary endpoint was the proportion of patients achieving an NRS pain score of less than 4 out of 10 (from a baseline score of at least 7 out of 10). The principle secondary outcome measure was the Roland-Morris Disability Questionnaire (RDQ)¹² consisting of 24 questions about dysfunctions in daily activities experienced by patients with back pain. Scores range from 0 to 24, with higher numbers indicating worse physical functioning. Other secondary outcomes included scores for the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO)¹³ and the European Quality of Life-5 Dimensions (EQ-5D).¹⁴ Analgesic consumption recorded the use of analgesic medication within the previous 24 h. Visual Analogue Scale (VAS) pain and a timed up-and-go test¹⁵ were done during three clinic visits (baseline, 2 weeks, and 6 months). Duration of hospital stay was recorded for participants who were hospital inpatients at time of enrolment. Participants who were outpatients at enrolment were not admitted to hospital.

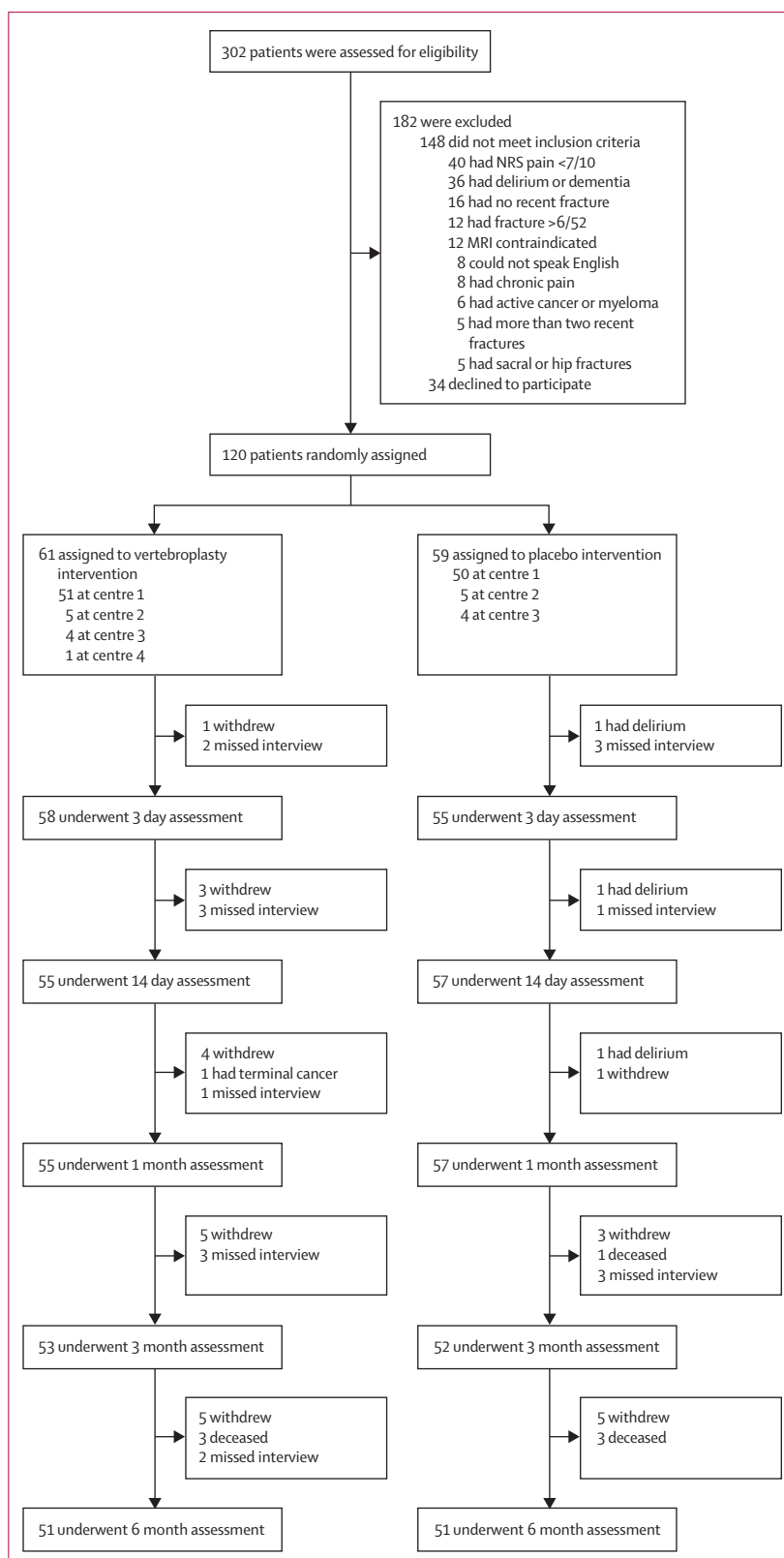


Figure 1: Trial profile

Patients who missed one interim assessment could be included in subsequent assessments. NRS=Numeric Rated Scale.

	Vertebroplasty (n=61)	Placebo (n=59)
Age (years)	80 (7)	81 (7)
Sex		
Male	13 (21%)	19 (32%)
Female	48 (79%)	40 (68%)
Hospital inpatient	34 (56%)	34 (58%)
Previous osteoporotic fractures	36 (62%)	32 (54%)
Medications for osteoporosis		
Any	48 (79%)	51 (86%)
Calcium or vitamin D	41 (70%)	48 (81%)
Bisphosphonates	29 (49%)	21 (36%)
Bone mineral density (T score)		
Lumbar spine	-4.1 (1.1)	-4.5 (0.9)
Femoral neck	-2.2 (0.7)	-2.2 (1.0)
Serum vitamin D (nmol/L)	70 (27)	73 (22)
Duration of fracture		
Mean (SD; weeks)	2.8 (1.6)	2.4 (1.4)
1-3 weeks	47 (77%)	48 (81%)
4-6 weeks	14 (23%)	11 (19%)
Spinal segment of fracture		
Thoracic (T4-T10)	19 (31%)	16 (27%)
Thoracolumbar (T11-L2)	37 (61%)	36 (61%)
Lumbar (L3-L5)	7 (12%)	10 (17%)
Vertebral body height loss (percentage points)	47 (15)	46 (15)
Genant grade (standing)		
Grade 1	3 (5%)	8 (14%)
Grade 2	13 (21%)	12 (20%)
Grade 3	45 (74%)	39 (66%)
Number of vertebral bodies treated		
1	51 (84%)	53 (90%)
2	10 (16%)	6 (10%)
Opioids for pain	53 (87%)	53 (90%)
Pain intensity during previous 24 h		
NRS score	8.6 (1.3)	8.6 (1.2)
VAS score	81 (18)	82 (15)
RDQ score	19.5 (3.5)	19.8 (3.7)
EQ-5D score	0.60 (0.07)	0.59 (0.06)
QUALEFFO score	65.4 (11.4)	67.7 (11.2)
Timed up-and-go score	26 (14)	29 (15)

Data are n (%) or mean (SD). Bone mineral density T score measured by quantitative computed tomography. NRS=Numeric Rating Scale pain. VAS=Visual Analogue Scale pain. RDQ=Roland-Morris Disability Questionnaire. EQ-5D=EuroQol five dimensions questionnaire. QUALEFFO=Quality of Life questionnaire of the European Foundation for Osteoporosis.

Table 1: Baseline characteristics

To assess masking efficacy, patients were asked on day 14 to guess which procedure they had undergone, rate their confidence in the guess as a percentage, and nominate the main reason for their guess. The outcome assessor answered similar questions based on observed changes in patient mobility and apparent pain since baseline.

We made changes to some outcome measures after trial commencement. We removed a planned SF-36 Health Survey at all timepoints and QUALEFFO at 3 days and 3 months to shorten the questionnaires. We added the questionnaire to assess masking efficacy. Outcome assessors had reported that some sick, elderly patients had difficulty completing the long questionnaires, so they prioritised the key outcomes of NRS pain and RDQ before other scores with medication history and the masking efficacy questionnaire at the end.

Written outcome data were obtained, converted to an electronic format, and stored by Optimus Clinical Research Pty Ltd. Data were masked until data collection was complete. At completion, the data were unmasked by independent statisticians who provided a study report. No interim analyses were done.

Calibrated standing spinal radiographs were obtained at baseline and 6 months to measure vertebral body height and incident vertebral fractures. Fractured vertebral body height was measured at anterior, middle, and posterior thirds. The smallest of these measures was divided by the height of the anterior cortex of the closest normal vertebral body to determine height loss percentage and Genant score.¹⁶ Interval change of vertebral height loss from baseline to 6 months was calculated. If there were two acute vertebral fractures, the fracture showing maximum height change was included in this analysis. Incident fracture was defined as a normal vertebral body at baseline that was deformed by at least 15% height loss on the 6 month image. Two radiologists assessed these measurements by consensus.

Statistical analysis

EB and VG did the statistical analyses at the NHMRC Clinical Trials Centre, University of Sydney. We calculated that a sample size of 60 patients per group would have greater than 80% power and 95% confidence to detect a difference in the primary outcome from 35% in the control group to 65% in the active group, allowing for a modest loss to follow-up.

Effectiveness analyses were done for all patients with available outcome data by the intention-to-treat principle according to their assigned group. Proportions were compared with a two-sided χ^2 test. Changes in quality of life measures (pain and functional disability scores) were analysed with *t* tests to enable comparisons with published studies, and non-parametric tests or regression modelling techniques depending on the distribution of the data. All comparisons were two-sided with a significance level of 5% considered as being statistically significant. Measures of effect are presented as either risk differences or mean differences together with the respective 95% CIs. Given full compliance with randomised treatment, the safety group was the same as the intention-to-treat group.

Prespecified subgroup analysis was done according to fracture position by spinal segment and also according to

fracture age (≤ 3 weeks, > 3 weeks). Spinal segments were thoracic (T5 to T10), thoracolumbar (T11 to L2), and lumbar (L3 to L5). Binary logistic regression was used to estimate the effects of subgroup factor, randomised treatment, and their interaction. SAS 9.3 was used for the statistical analysis. The study is registered with ClinicalTrials.gov, number NCT01482793.

Role of the funding source

The study was funded by an unrestricted educational grant from CareFusion Corporation (San Diego, CA, USA). CareFusion Corporation had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

Results

Between Nov 4, 2011, and Dec 5, 2014, 120 patients were enrolled, randomly assigned, and all underwent the assigned intervention (figure 1). Baseline characteristics of both groups were similar (table 1). The mean PMMA volume injected per bone was 7.5 mL (SD 2.8). Minor PMMA extravasation occurred in 21 (34%) of 61 patients. 112 (93%) of 120 patients completed follow-up at 14 days and 102 (85%) had final assessment at 6 months.

In the intention-to-treat analysis, the proportion of patients with NRS pain of less than 4 out of 10 at 14 days was 44% (24 of 55 patients) in the vertebroplasty group and 21% (12 of 57 patients) in the control group (between-group difference 23 percentage points, 95% CI 6–39; $p=0.011$). The advantage for the vertebroplasty group persisted at all data collection timepoints to 6 months, with a maximum between-group difference at 4 weeks of 33 percentage points (95% CI 17–50; table 2, figure 2).

Mean reduction in NRS pain was greater in the vertebroplasty group compared with the control group at all timepoints (maximum between-group difference was 1.8 [95% CI 0.8–2.7] at 3 days, and remained 1.3 [95% CI 0–2.6] at 6 months; table 2, appendix). Patient-reported VAS pain, completed by fewer patients (88) at 14 days, attributable to telephone interview replacing clinic attendance, was lower in the vertebroplasty group than in the control group at 6 months but not at 14 days (table 2). Researcher-observed VAS pain was lower in the vertebroplasty group than in the control group at 14 days but not at 6 months (table 2, appendix). Mean reduction in RDQ score was greater in the vertebroplasty group than in the control group at 1 month, 3 months, and 6 months, but not at 3 days and 14 days, with between-group differences increasing at successive timepoints to a maximum of 4.2 (95% CI 1.6 to 6.9) at 6 months (table 2, appendix). QUALEFFO score was lower in the vertebroplasty group than in the control group at 14 days and 6 months but not at 1 month (table 2, appendix). EQ-5D score was higher in the vertebroplasty group than in the control group at

	Vertebroplasty		Placebo		Difference (95% CI)	p value
	N	n (%) or mean (SD)	N	n (%) or mean (SD)		
Proportion of patients with NRS pain score <4						
3 days	58	18 (31%)	55	5 (9%)	22 (8 to 36)	0.004
14 days*	55	24 (44%)	57	12 (21%)	23 (6 to 39)	0.011
1 month	55	28 (51%)	57	10 (18%)	33 (17 to 50)	0.0002
3 months	53	29 (55%)	52	17 (33%)	22 (4 to 41)	0.023
6 months	51	35 (69%)	51	24 (47%)	22 (3 to 40)	0.027
Reduction in NRS pain score						
3 days	58	3.5 (2.6)	55	1.8 (2.3)	1.8 (0.8 to 2.7)	0.0003
14 days	55	4.2 (2.7)	57	3.0 (3.0)	1.2 (0.1 to 2.3)	0.026
1 month	55	4.6 (3.0)	57	3.2 (2.7)	1.4 (0.4 to 2.5)	0.010
3 months	53	5.4 (3.5)	52	4.1 (3.1)	1.3 (0 to 2.6)	0.047
6 months	51	6.1 (3.3)	51	4.8 (3.1)	1.3 (0 to 2.6)	0.043
Reduction in RDQ score						
3 days	58	4.5 (6.2)	55	2.9 (4.4)	1.6 (–0.4 to 3.6)	0.111
14 days	53	5.9 (5.8)	56	4.1 (6.3)	1.8 (–0.5 to 4.1)	0.121
1 month	55	6.9 (6.0)	54	4.3 (5.6)	2.6 (0.4 to 4.8)	0.021
3 months	53	9.6 (7.7)	50	6.4 (7.0)	3.2 (0.3 to 6.1)	0.031
6 months	49	11.7 (6.5)	51	7.4 (6.9)	4.2 (1.6 to 6.9)	0.0022
VAS pain score (patient reported)						
14 days	41	39 (28)	47	49 (28)	10 (–2 to 22)	0.096
6 months	42	23 (26)	46	34 (27)	11 (0 to 23)	0.050
VAS pain score (researcher observed)						
14 days	41	25 (23)	48	39 (29)	14 (3 to 26)	0.015
6 months	39	14 (21)	46	19 (20)	5 (–4 to 13)	0.301
QUALEFFO score						
14 days	48	49 (13)	54	55 (14)	6 (1 to 11)	0.029
1 month	48	49 (17)	52	52 (15)	4 (–3 to 10)	0.255
6 months	46	38 (15)	48	45 (16)	7 (1 to 13)	0.032
EQ-5D score						
3 days	58	0.69 (0.11)	52	0.65 (0.09)	–0.03 (–0.07 to 0.05)	0.091
14 days	49	0.69 (0.10)	56	0.68 (0.11)	–0.01 (–0.06 to 0.03)	0.471
1 month	47	0.75 (0.11)	51	0.70 (0.11)	–0.05 (–0.09 to 0)	0.043
3 months	51	0.75 (0.12)	49	0.71 (0.11)	–0.03 (–0.08 to 0.01)	0.164
6 months	47	0.80 (0.11)	50	0.74 (0.12)	–0.06 (–0.10 to –0.01)	0.012
Analgesic use						
3 days	59	57 (97%)	57	56 (98%)	2 (–4 to 7)	0.579
14 days	56	49 (88%)	57	52 (91%)	4 (–8 to 15)	0.520
1 month	55	41 (75%)	57	50 (88%)	13 (–1 to 28)	0.074
3 months	53	34 (64%)	53	44 (83%)	19 (2 to 35)	0.028
6 months	50	29 (58%)	51	39 (76%)	18 (1 to 36)	0.048

Data presented as mean (SD) were normally distributed. NRS=Numeric Rating Scale pain. RDQ=Roland-Morris Disability Questionnaire. VAS=Visual Analogue Scale pain. QUALEFFO=Quality of Life questionnaire of the European Foundation for Osteoporosis. EQ-5D=EuroQol five dimensions questionnaire. *Primary endpoint was the proportion of patients with an NRS pain score less than 4 at 14 days.

Table 2: Primary and secondary outcomes

1 month and 6 months, but not at 3 days, 14 days, or 3 months (table 2, appendix). A timed up-and-go test was completed by only 55 (46%) patients at baseline because of the patients inability to safely mobilise without assistance and there was no difference between groups at 14 days or 6 months (data not shown).

See Online for appendix

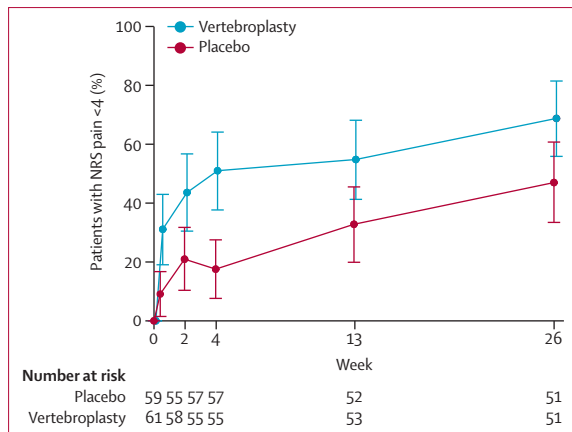


Figure 2: Proportion of patients in each group with Numeric Rated Scale (NRS) pain intensity of less than 4 out of 10
 Results are shown for 3 days, 14 days, 1 month, 3 months, and 6 months after the intervention. Vertical bars are 95% CIs. The primary outcome was the proportion of patients with an NRS pain score of less than 4 out of 10 at 2 weeks.

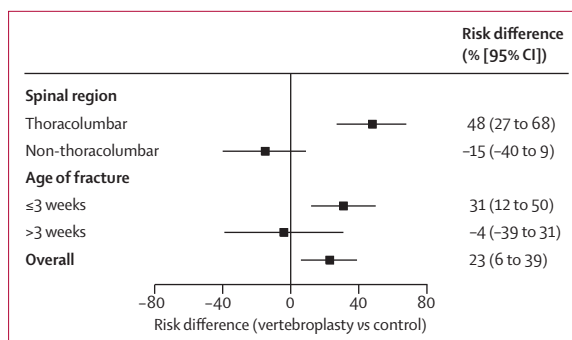


Figure 3: Prespecified subgroup outcomes
 Risk difference (percentage points) of meeting the primary endpoint of a Numeric Rated Scale pain score less than 4 out of 10, at 14 days after the procedure. Positive numbers favour vertebroplasty and negative numbers favour placebo.

The only analgesic outcome available for all 102 patients completing the 6-month follow-up was use of analgesic medication within the previous 24 h, which showed a reduction in the vertebroplasty group at 3 months and 6 months but not at 3 days, 14 days, or 1 month (table 2, appendix). Specific analgesic type was recorded for 68 patients at 6 months and showed no difference in opiate use between groups (data not shown).

For inpatients, median time from hospital admission to procedure was 6 days (IQR 4–10) in the vertebroplasty group and 6 days (3–9) in the control group. Median duration of hospital stay after the procedure was 8.5 days (IQR 4–13) in the vertebroplasty group and 14 days (7–22) in the control group.

At day 14, 54% (19 of 35) of the control group correctly guessed they had received a placebo with 58% degree of certainty, 80% (28 of 35) nominated change in pain as the main reason for their choice, 20% (seven of 35) chose another reason, and one patient indicated un-masking (by a radiography report). 80% (28 of 35) of the

vertebroplasty group correctly guessed that they had undergone vertebroplasty with 76% degree of certainty, 88% (31 of 35) nominated change in pain as the main reason for their choice, 11% (four of 35) chose another reason, and none indicated un-masking. Masked researchers correctly guessed that 50% (21 of 42) of the control group had undergone placebo intervention with 58% certainty and correctly guessed that 66% (25 of 38) of the vertebroplasty group had undergone vertebroplasty with 72% certainty.

Baseline and 6-month radiographs were available for 84 (41 vertebroplasty and 43 control) of the 102 patients who completed the 6-month follow-up. Baseline mean fracture height loss was similar in both groups (table 1). At 6 months the mean height loss was 27% (SD 12) in the vertebroplasty group and 63% (17) in the control group (between-group difference 36 percentage points, 95% CI 30–43; appendix). Three patients in the vertebroplasty group sustained single interval fractures and two patients in the control group sustained two and five incident fractures, respectively.

Subgroup analyses of the primary outcome were done at day 14. Outcome results were available for 64 patients with thoracolumbar fractures and 43 patients with non-thoracolumbar fractures. Five patients with two fractures involving both regions were excluded. In the thoracolumbar fracture subgroup, 20 (61%) of 33 patients in the vertebroplasty group versus four (13%) of 31 in the control group met the primary endpoint (between-group difference 48 percentage points, 95% CI 27–68). In the non-thoracolumbar fracture subgroup, three (15%) of 20 patients in the vertebroplasty group versus seven (30%) of 23 patients in the control group met this endpoint (between-group difference -15 percentage points, 95% CI -40 to 9; figure 3). A logistic regression model showed strong evidence ($p=0.0012$) of different treatment outcomes between these spinal segments. Day 14 results were available for 86 patients with fractures of 3 weeks' or less duration and 24 patients with fractures longer than 3 weeks with no significant difference ($p=0.12$) in treatment outcomes between these two subgroups (figure 3).

Three patients in each group died from causes judged unrelated to the procedure. In the vertebroplasty group there were two serious adverse events related to the procedure. One patient had a respiratory arrest after administration of sedation, before starting the procedure. The patient was resuscitated and underwent the trial procedure 2 days later without incident. One patient sustained a supracondylar humerus fracture in a paretic arm during transfer onto the radiology table. The fracture healed with a plaster cast. In the control group there were two serious adverse events related to the fracture. Both patients developed spinal cord compression due to interval collapse and retropulsion of the fracture several weeks after enrolment. Neither had substantial fracture retropulsion at time of

enrolment. One patient underwent spinal decompressive surgery with resolution of the neurological deficit. The other patient, not considered a surgical candidate, became paraplegic.

Discussion

Vertebroplasty was used to control acute, severe pain in an elderly, fragile patient group and was more effective than placebo in reducing pain from osteoporotic fractures within 6 weeks of onset. Enrolment required severe NRS pain (defined as a score of ≥ 7 out of 10) and clear success from vertebroplasty was designated as low NRS pain (defined as < 4 out of 10) at 14 days. The 23% advantage in this outcome was smaller than the 30% targeted in the study design, although this figure is within the CIs. The advantage would probably be greater if vertebroplasty were compared with usual care, where the control group would not benefit from the placebo effect. In the context of poor outcomes in the control group, we regard this benefit as clinically important. Repeated measures analysis was not done but we noted sustained benefit in the vertebroplasty group at all timepoints to 6 months. At 6 months, 53% (27 of 51) of patients in the control group still had moderate or severe pain and 76% (39 of 51) were still using analgesic medication.

Mean NRS pain score, the primary endpoint nominated in previous masked trials, was lower in the vertebroplasty group at all timepoints after the procedure. Mean pain score measures overall pain burden in each group but not the proportion of patients deriving the desired clinical benefit, which our primary endpoint measured directly. Other benefits were reduced mean RDQ at 1 month, 3 months, and 6 months, and a reduced proportion of patients using analgesic medications at 3 months and 6 months. Mean VAS pain score, completed by fewer patients, had a smaller change than the NRS pain score. Differences in QUALEFFO and EQ-5D scores were small and inconsistent but with trends favouring vertebroplasty.

Two serious adverse events from vertebroplasty procedures were balanced by two cases of spinal cord compression from progressive vertebral body collapse in the control group. These cases of spinal compression highlight the risks associated with painful, osteoporotic, spinal fractures. Previous RCTs^{4,5,7} have not found significant increases in adverse outcomes with vertebroplasty. There was no difference in new fracture incidence between the two groups. A systematic review⁷ of trials reporting new fracture incidence following vertebroplasty showed no change compared with usual care.

The patients in our trial were older, with higher pain scores, and increased disability at enrolment than those in previous masked trials.^{4,5} Hospital inpatients constituted 57% of enrolled patients in this study, indicating severe disability. For these inpatients, median duration of hospital stay was reduced by 5.5 days in the vertebroplasty group. Attending physicians were masked as to the procedure so that discharge decisions were based on clinical improvement rather than treatment

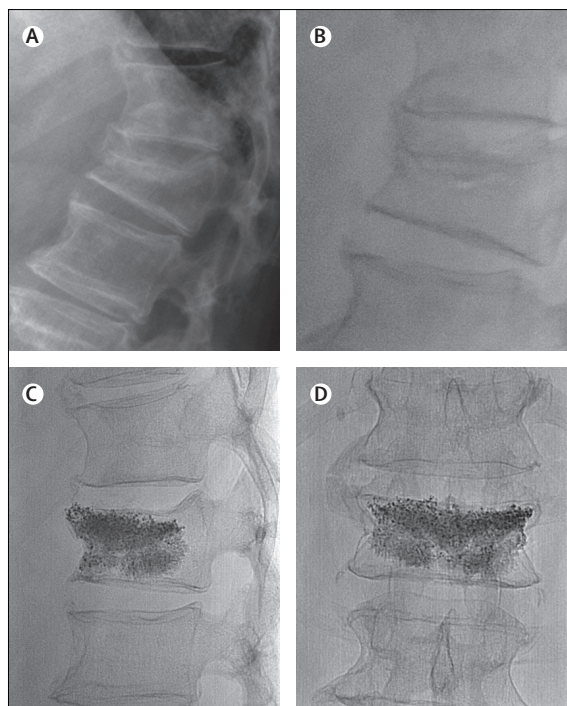


Figure 4: Vertebral fill technique

Images are of a man aged 74 years with a 10-day-old L1 fracture. (A) Erect baseline radiograph with substantial anterior compression. (B) Fluoroscopic image immediately before vertebroplasty with improved vertebral height in the prone position (dynamic mobility). There is gas in the fracture cleft adjacent to the superior vertebral body endplate. Lateral (C) and frontal (D) radiographs in the prone position, immediately after vertebroplasty with 10 mL of polymethylmethacrylate (PMMA) injected. There is denser PMMA in the fracture cleft and less dense trabecular PMMA in the bone below the cleft to support the vertebral body against collapse in the erect position. The PMMA distributes from the superior to the inferior end-plate, from the anterior cortex into the posterior third of the vertebral body, and from at least mid-pedicle to mid-pedicle in the frontal projection from top to bottom. We describe this pattern as adequate vertebral fill. In this case it has partially reduced the fracture, augmenting vertebral body height.

allocation. Reduced duration of hospital stay with vertebroplasty has been reported previously.⁸

At 6 months there was a 36 percentage point difference in mean vertebral body height between the two groups, due to similar measures of augmentation from vertebroplasty and interval collapse in the control group. PMMA is more radiopaque than bone so could result in over-estimation of vertebral body height and these measures were unmasked. Vertebroplasty has been previously shown to improve vertebral body height.^{18,19}

Benefits from vertebroplasty were concentrated in the thoracolumbar fracture subgroup, where 48% more patients in the vertebroplasty group met the primary endpoint than in the placebo group. Conversely, there was no benefit from vertebroplasty over placebo in the non-thoracolumbar subgroup. The thoracolumbar junction lies between the inflexible thoracic and flexible lumbar segments, subjecting it to increased dynamic load. Thoracolumbar fractures have the highest incidence of dynamic mobility²⁰ (changing degrees of fracture

compression in different postures) and fracture clefts²¹ (defects containing gas or fluid within the fracture).

Placebo in previous masked trials included anaesthetising the posterior vertebral cortex, raising questions of potential therapeutic rather than placebo effect.²² We confined local anaesthesia subcutaneously. Previous trials used PMMA kits that generated a strong odour during mixing, which necessitated kits be opened during placebo procedures to prevent the patient guessing their procedure by smell. The kit used in our trial is virtually odourless, with a closed mixing and delivery system, and was not opened during placebo procedures—patients could not smell, hear, or see it. We otherwise replicated the masking process used in the INVEST trial,⁴ a key component of which was adequate conscious sedation, which in this elderly group often causes procedural amnesia.

An adequate fill of PMMA was that volume required to meet our endpoints for cement distribution as defined in Methods and shown in figure 4. This amount can support the bone against collapse and might partly reduce the fracture (figure 4). PMMA volume was higher than reported in previous RCTs^{5,7} because of shorter fracture duration, a high viscosity PMMA, and our adequate fill technique. Mean fracture age and PMMA volume were 2·6 weeks and 7·5 mL in this trial, 5·6 weeks and 4·1 mL in the VERTOS2 trial,⁷ and 11·7 weeks and 2·8 mL in a masked trial.^{5,10} The plasticity of fractures within 6 weeks of onset allows larger volumes of PMMA to be injected with reduced resistance. Minor PMMA extravasation occurred in 21 (34%) patients in the vertebroplasty group, comparing favourably with other RCTs.^{5,7} In less acute fractures, extravasation might occur with small volumes.²³

Before beginning our trial, a systematic literature review by the Australian Medicare Services Advisory Committee²⁴ concluded that two placebo-controlled trials provided good evidence for lack of efficacy of vertebroplasty but noted under-representation of patients with a fracture duration less than 6 weeks in these trials. A more recent systematic review of vertebroplasty²⁵ included six unmasked RCTs comparing vertebroplasty with usual care and two masked RCTs comparing vertebroplasty with placebo. Of these, only two open RCTs were designed for patients with fractures of less than 6 weeks' duration with both trials showing greater pain relief with vertebroplasty than with usual care. The review concluded that vertebroplasty was not effective, on the basis of the negative outcomes of two masked trials that enrolled patients with fractures of up to 12 months' duration. Subgroup meta-analysis¹⁰ of pooled data from both trials analysed 57 patients (25 vertebroplasty and 32 placebo) with pain less than 6 weeks' duration, finding no benefit from vertebroplasty in this subgroup, but there were limitations compared with our trial. The number of patients was small, technical data (PMMA volume and fracture location) were not presented, inpatients were not included, and outcome results beyond 1 month were not

presented. Our trial was specifically designed for patients with fractures of less than 6 weeks' duration (including inpatients and outpatients) and had more than twice the number of patients than this subgroup meta-analysis, providing enhanced statistical power.

Kyphoplasty is a similar intervention to vertebroplasty but has an additional step of inflating balloons via the needles in the vertebral body to create cavities before injection of PMMA. A large unmasked RCT²⁶ of kyphoplasty versus usual care in patients with fractures of less than 3 months' duration found kyphoplasty effective in improving quality of life, pain, and disability. Three RCTs^{18,27,28} comparing vertebroplasty with kyphoplasty and a systematic review and meta-analysis²⁹ of trials comparing vertebroplasty and kyphoplasty have reported equivalent improvements in clinical outcomes with both techniques.

Our study had some limitations. Eight patients (six vertebroplasty and two placebo) did not have day 14 outcome measures because of revoking consent, delirium, or not being contactable. If all were included in the analysis and presumed to be treatment failures, there would be a minor effect on primary outcome (between-group difference 19 percentage points, 95% CI 3–35; $p=0\cdot023$). 20 patients (11 vertebroplasty and nine placebo) were unable to attend the clinic at day 14 and were interviewed by telephone. The NRS pain question did not change so this should not have affected the primary outcome. 85% of the procedures were done in one centre. Centres with high procedure rates can have superior outcomes³⁰ possibly affecting the generalisability of our findings. This proportion is not greatly dissimilar to one masked trial⁵ where 68% (53 of 78) of procedures were done in one centre and 87% (68 of 78) in two centres, but is quite different to the other masked trial⁴ in this regard. Recruitment in three of our centres proved difficult, as for previous placebo trials, and they failed to meet their enrolment targets.

Our trial had a higher proportion (78% [120 of 154]) of eligible patients who enrolled compared with previous masked trials, reducing potential selection bias. This high enrolment was facilitated by the precedent of two placebo-controlled trials, termination of vertebroplasty funding in Australia in 2011, and by the four centres not offering vertebroplasty outside the trial. Patients with severe pain had a choice between enrolling in the trial or conservative therapy and most chose enrolment. The absence of a crossover option was another strength of our trial, compared with the larger of the previous masked trials.⁴

In conclusion, our trial demonstrates clinical efficacy for vertebroplasty in reducing pain from osteoporotic spinal fractures of less than 6 weeks when compared with a true placebo control. Subgroup analysis suggests that most benefit from vertebroplasty is in the thoracolumbar spinal segment and further research is recommended to assess this finding.

Contributors

WC, PB, PG, THD, and VG contributed to the study design. WC, PB, PG, THD, PS, HPM, GS, and CB contributed to data collection. EB and VG did the statistical analysis. WC wrote the first draft of the manuscript. All authors contributed to final data interpretation and contributed to and approved the final draft of the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

The study was funded by an unrestricted research grant from CareFusion Corporation. We thank the patients, their partners, and families. We thank the researchers from Optimus Clinical Research. We thank the interventional radiology nurses and radiographers in the interventional radiology departments. We extend special thanks to L McGuigan (safety monitoring committee), C Dedousis, D Glenn, A Goh, P J Papantoniou, and T Harrington for their participation as investigators in the trial. We thank L Buizen for his work on the statistical analysis.

References

- Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006; **17**: 1726–33.
- Jacobsen SJ, Cooper C, Gottlieb MS, Goldberg J, Yahnke DP, Melton LJ. Hospitalization with vertebral fracture among the aged: a national population-based study, 1986–1989. *Epidemiology* 1992; **3**: 515–18.
- Goldstein CL, Chutkan NB, Choma TJ, Orr RD. Management of the elderly with vertebral compression fractures. *Neurosurgery* 2015; **77** (suppl 4): S33–45.
- Kallmes DF, Comstock BA, Heagerty PJ, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med* 2009; **361**: 569–79.
- Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med* 2009; **361**: 557–68.
- Boszczyk B. Volume matters: a review of procedural details of two controlled vertebroplasty trials of 2009. *Eur Spine J* 2010; **19**: 1837–40.
- Klazen CA, Lohle PN, de Vries J, et al. Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial. *Lancet* 2010; **376**: 1085–92.
- Rousing R, Andersen MO, Jespersen SM, Thomsen K, Lauritsen J. Percutaneous vertebroplasty compared to conservative treatment in patients with painful acute or subacute osteoporotic vertebral fractures: three-months follow-up in a clinical randomized study. *Spine* 2009; **34**: 1349–54.
- Rousing R, Hansen KL, Andersen MO, Jespersen SM, Thomsen K, Lauritsen JM. Twelve-months follow-up in forty-nine patients with acute/semiacute osteoporotic vertebral fractures treated conservatively or with percutaneous vertebroplasty: a clinical randomized study. *Spine* 2010; **35**: 478–82.
- Staples MP, Kallmes DF, Comstock BA, et al. Effectiveness of vertebroplasty using individual patient data from two randomised placebo controlled trials: meta-analysis. *BMJ* 2011; **343**: d3952.
- Clark WA, Bird P, Diamond TH, Gonski PN. Vertebroplasty for acute painful osteoporotic fractures (VAPOUR): study protocol for a randomized controlled trial. *Trials* 2015; **16**: 159.
- Roland M, Fairbank J. The Roland–Morris Disability Questionnaire and the Oswestry Disability Questionnaire. *Spine* 2000; **25**: 3115–24.
- Lips P, Cooper C, Agnusdei D, et al. Quality of life in patients with vertebral fractures: validation of the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO). Working Party for Quality of Life of the European Foundation for Osteoporosis. *Osteoporosis Int* 1999; **10**: 150–60.
- Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol group. *Ann Med* 2001; **33**: 337–43.
- Podsiadlo D, Richardson S. The timed “Up and Go”: a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991; **39**: 142–48.
- Genant HK, Wu CY, van Kujik C, Nevitt MC. Vertebral fracture assessment using a semi-quantitative technique. *J Bone Miner Res* 1993; **8**: 1137–48.
- Han SL, Wan SL, Li QT, et al. Is vertebroplasty a risk factor for subsequent vertebral fracture, meta-analysis of published evidence? *Osteoporos Int* 2015; **26**: 113–22.
- Liu JT, Liao WJ, Tan WC, et al. Balloon kyphoplasty versus vertebroplasty for treatment of osteoporotic vertebral compression fracture: a prospective, comparative, and randomized clinical study. *Osteoporos Int* 2010; **21**: 359–64.
- Klazen CAH, Venmans A, de Vries J, et al. Percutaneous vertebroplasty is not a risk factor for new osteoporotic compression fractures—results from VERTOS II. *Am J Neuroradiol* 2010; **31**: 1447–50.
- McKiernan F, Jensen R, Faciszewski T. The dynamic mobility of vertebral compression fractures. *J Bone Miner Res* 2003; **18**: 24–29.
- McKiernan F, Faciszewski T. Intravertebral clefts in osteoporotic vertebral compression fractures. *Arthritis Rheum* 2003; **48**: 1414–19.
- Wilson DJ, Owen S, Corkill RA. Facet joint injections as a means of reducing the need for vertebroplasty in insufficiency fractures of the spine. *Eur Radiol* 2011; **21**: 1772–78.
- Kroon F, Staples M, Ebeling PR, et al. Two-year results of a randomized placebo-controlled trial of vertebroplasty for acute osteoporotic vertebral fractures. *J Bone Miner Res* 2014; **29**: 1346–55.
- Doidge J, Merlin T, Liufu Z, Tamblin D, Jia LY, Hiller JE. Review of interim funded service: vertebroplasty and new review of Kyphoplasty. MSAC Application 27.1. Canberra, ACT: Commonwealth of Australia, 2011. <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/271-public> (accessed June 15, 2016).
- Buchbinder R, Golmohammadi K, Johnston RV, et al. Percutaneous vertebroplasty for osteoporotic vertebral compression fracture. *Cochrane Database Syst Rev* 2015; **4**: CD006349.
- Wardlaw D, Cummings SR, Van Meirhaeghe J, et al. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. *Lancet* 2009; **373**: 1016–24.
- Evans AJ, Kip KE, Brinjikji W, et al. Randomized controlled trial of vertebroplasty versus kyphoplasty in the treatment of vertebral compression fractures. *J NeuroInterv Surg* 2015; published online June 24. DOI:10.1136/neurintsurg-2015-011811.
- Dohm M, Black CM, Dacre A, Tillman JB, Fueredi G. A randomized trial comparing balloon kyphoplasty and vertebroplasty for vertebral compression fractures due to osteoporosis. *Am J Neuroradiol* 2014; **35**: 2227–36.
- Gu CN, Brinjikji W, Evans AJ, Murad MH, Kallmes DF. Outcomes of vertebroplasty compared with kyphoplasty: a systematic review and meta-analysis. *J Neurointerv Surg* 2016; **8**: 636–42.
- Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med* 2008; **148**: 295–309.