The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 6, 2009 VOL. 361 NO. 6

A Randomized Trial of Vertebroplasty for Painful Osteoporotic Vertebral Fractures

Rachelle Buchbinder, Ph.D., Richard H. Osborne, Ph.D., Peter R. Ebeling, M.D., John D. Wark, Ph.D., Peter Mitchell, M.Med., Chris Wriedt, M.B., B.S., Stephen Graves, D. Phil., Margaret P. Staples, Ph.D., and Bridie Murphy, B.Sc.

ABSTRACT

BACKGROUND

Vertebroplasty has become a common treatment for painful osteoporotic vertebral fractures, but there is limited evidence to support its use.

METHODS

We performed a multicenter, randomized, double-blind, placebo-controlled trial in which participants with one or two painful osteoporotic vertebral fractures that were of less than 12 months' duration and unhealed, as confirmed by magnetic resonance imaging, were randomly assigned to undergo vertebroplasty or a sham procedure. Participants were stratified according to treatment center, sex, and duration of symptoms (<6 weeks or ≥6 weeks). Outcomes were assessed at 1 week and at 1, 3, and 6 months. The primary outcome was overall pain (on a scale of 0 to 10, with 10 being the maximum imaginable pain) at 3 months.

RESULTS

A total of 78 participants were enrolled, and 71 (35 of 38 in the vertebroplasty group and 36 of 40 in the placebo group) completed the 6-month follow-up (91%). Vertebroplasty did not result in a significant advantage in any measured outcome at any time point. There were significant reductions in overall pain in both study groups at each follow-up assessment. At 3 months, the mean (±SD) reductions in the score for pain in the vertebroplasty and control groups were 2.6±2.9 and 1.9±3.3, respectively (adjusted between-group difference, 0.6; 95% confidence interval, −0.7 to 1.8). Similar improvements were seen in both groups with respect to pain at night and at rest, physical functioning, quality of life, and perceived improvement. Seven incident vertebral fractures (three in the vertebroplasty group and four in the placebo group) occurred during the 6-month follow-up period.

CONCLUSIONS

We found no beneficial effect of vertebroplasty as compared with a sham procedure in patients with painful osteoporotic vertebral fractures, at 1 week or at 1, 3, or 6 months after treatment. (Australian New Zealand Clinical Trials Registry number, ACTRN012605000079640.)

From the Monash Department of Clinical Epidemiology, Cabrini Hospital, and the Department of Epidemiology and Preventive Medicine, Monash University, Malvern, VIC (R.B., M.P.S., B.M.); Public Health Innovation, Deakin University, Melbourne, VIC (R.H.O.); the Department of Medicine (Royal Melbourne Hospital/Western Hospital), University of Melbourne Western Hospital, Footscray, VIC (P.R.E.); the Department of Medicine (Royal Melbourne Hospital/Western Hospital) and the Department of Radiology, University of Melbourne, Royal Melbourne Hospital, Parkville, VIC (J.D.W., P.M.); Cabrini Medical Imaging, Cabrini Health, Malvern, VIC (C.W.); and the Australian Orthopaedic Association, National Joint Replacement Register, Data Management & Analysis Centre, University of Adelaide, Adelaide, SA (S.G.) — all in Australia. Address reprint requests to Dr. Buchbinder at the Department of Clinical Epidemiology, Suite 41 Cabrini Medical Centre, 183 Wattletree Rd., Malvern, VIC 3144, Australia, or at rachelle.buchbinder@med.monash.edu.au.

N Engl J Med 2009;361:557-68.

Osteoporotic vertebral fractures are a common cause of pain and disability and are associated with increased mortality.[1] Approximately 750,000 new vertebral fractures occur in the United States each year,[2] and among people who are older than 50 years of age, up to a quarter of them will have at least one vertebral fracture in their lifetime.[3] Although most fractures heal within a few months, some people have pain and disability that fail to respond to conservative therapy, and some require hospitalization, long-term care, or both.[4] Therefore, interventions that effectively manage pain and shorten recovery time would be of great benefit.

Vertebroplasty, the percutaneous injection of polymethylmethacrylate (PMMA) into the affected vertebral body, has been advocated as a treatment for painful osteoporotic vertebral fractures.[5,6] Observational studies suggest that there is an immediate and sustained reduction in pain after this procedure is performed,[5] but data from high-quality randomized, controlled trials are lacking. The best currently available evidence for the efficacy of vertebroplasty comes from one randomized, open trial involving 34 patients[7] and two quasi-experimental, open, controlled, before–after studies that compared vertebroplasty with conservative treatment.[8,9] Although each study showed an early benefit of vertebroplasty, methodologic weaknesses cast doubt on the findings. In particular, the lack of blinding and the lack of a true sham control raise concern that the observed benefits reflected a placebo response, an effect that may be magnified with an invasive procedure.[10] The same caveat applies to a recently published, open, randomized trial of balloon kyphoplasty, a procedure in which a balloon is used to inflate the affected vertebral body in order to compact the bone and push the end plates apart before the void is filled with bone cement.[11]

Despite evidence that is acknowledged to be inadequate as a basis for justifying reimbursement, public institutions have recommended reimbursement for vertebroplasty.[12,13] A recent position statement from various American radiologic and neurologic surgical societies also recommended funding the procedure.[6] These endorsements have resulted in a dramatic increase in the number of vertebroplasties performed.[14,15] For example, an examination of aggregate fee-for-service data from U.S. Medicare enrollees for the period from 2001 through 2005 showed that the rate of vertebroplasties performed during that time almost doubled, from 45.0 to 86.8 per 100,000 enrollees.[14] There are also reports of repeat procedures for unrelieved pain at previously treated vertebral levels[16] and of the prophylactic use of vertebroplasty in normal vertebrae that were deemed to be at high risk for fracture.[17]

Not only is the short-term efficacy of vertebroplasty unproven, but there are also several uncontrolled studies suggesting that vertebroplasty may increase the risk of subsequent vertebral fractures, particularly in vertebrae that are adjacent to treated levels, sometimes after cement has leaked into the adjacent disk[18]; controlled studies have shown conflicting results.[8,9] Currently, there are insufficient data to estimate the true risk of subsequent vertebral fracture after vertebroplasty.[18]

METHODS

STUDY DESIGN

We performed a randomized, parallel-group, placebo-controlled trial to determine the short-term efficacy and safety of vertebroplasty for alleviating pain and improving physical functioning in persons with painful osteoporotic vertebral fractures. The protocol has been reported previously.[19] The participants, investigators (other than the radiologists performing the procedures), and outcome assessors were unaware of the group assignments. A 2-year follow-up period was planned. Enrollment commenced in April 2004 and concluded at the end of October 2008, and the follow-up period will end in October 2010. The human research ethics committee at each participating center approved the study, and all participants provided written informed consent. Cook Australia provided partial grant support but had no role in the design of the trial, the collection or analysis of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication.

PARTICIPANTS

Participants were recruited from the practices of general practitioners and specialists and from hospital inpatient and emergency departments. Inclusion criteria were the presence of back pain of no more than 12 months' duration and the presence of one or two recent vertebral fractures, defined as vertebral collapse of grade 1 or higher according to the grading system of Genant et al.[20]

(in which vertebral collapse is graded on a scale of 0 to 3, with higher numbers indicating greater vertebral collapse), and edema, a fracture line, or both within the vertebral body on magnetic resonance imaging (MRI).[19] The presence of bone marrow edema indicates an acute fracture.[21]

The exclusion criteria were the presence of more than two recent vertebral fractures, spinal cancer, neurologic complications, osteoporotic vertebral collapse of greater than 90%, fracture through or destruction of the posterior wall, retropulsed bony fragment or bony fragments impinging on the spinal cord, medical conditions that would make the patient ineligible for emergency decompressive surgery if needed, previous vertebroplasty, inability to give informed consent, and a likelihood of noncompliance with follow-up.

Eligible participants were randomly assigned in permuted blocks of 4 and 6, according to computer-generated random numbers, to undergo either vertebroplasty or a sham procedure. Participants were stratified according to treatment center, sex, and duration of symptoms (<6 weeks or ≥6 weeks). To ensure concealment of the assigned intervention, the treating radiologist obtained the opaque, sealed envelope containing the participant's assigned intervention from the site's receptionist just before the procedure was performed. Only the receptionist had access to the site's assignment schedule. Neither the receptionist nor the treating radiologist had any other role in the trial.

INTERVENTIONS

There were four participating sites, and experienced interventional radiologists performed all procedures. All the radiologists had undertaken formal training in vertebroplasty, had appropriate certification, and were actively performing the procedure. All the radiologists strictly adhered to a detailed, standardized protocol. Care was taken to ensure that participants remained unaware of their assigned intervention.

For percutaneous vertebroplasty, the left pedicle of the fracture site was identified with the use of a metallic marker. A 25-gauge needle was used to infiltrate the skin overlying the pedicle, and a 23-gauge needle was used to infiltrate the periosteum of the posterior lamina. An incision was made in the skin, and a 13-gauge needle was placed posterolaterally relative to the eye of the pedicle. Gentle tapping guided the needle through the pedicle into the anterior two thirds of the fractured vertebral body. Anterior–posterior and lateral images were recorded with the needle in the correct position.

Prepared PMMA (approximately 3 ml) was slowly injected into the vertebral body, and satisfactory infiltration of the vertebral body was confirmed radiographically. A bipedicular approach was used only if there was inadequate instillation of cement with the unipedicular approach. Injection was stopped when substantial resistance was met or when the cement reached the posterior quarter of the vertebral body; injection was also stopped if cement leaked into extraosseous structures or veins. All participants in the vertebroplasty group received cephalothin, administered intravenously immediately after PMMA injection.

Participants who were assigned to the sham intervention underwent the same procedures as those in the vertebroplasty group up to the insertion of the 13-gauge needle to rest on the lamina. The central sharp stylet was then replaced with a blunt stylet. To simulate vertebroplasty, the vertebral body was gently tapped, and PMMA was prepared so that its smell permeated the room.

After the intervention, all participants received usual care. Treatment decisions were made at the discretion of the treating physician, who received up-to-date guidelines on the management of osteoporosis. Analgesia was given according to standard practice, and its use was recorded.

OUTCOME ASSESSMENT

Baseline data, which were collected by a blinded assessor, included sex, birth date, height, weight, risk factors for osteoporosis, smoking status and alcohol use, medication use, history of fractures, measurement of bone mineral density (current or within the previous year), and the nature of the vertebral fractures.[20] At baseline, each participant also underwent the Up and Go test, which measures the time required to rise from a standard arm chair, walk 3 m, turn around, return to the chair, and sit down again.[22] All participants were evaluated with the use of mailed questionnaires at 1 week and 1, 3, and 6 months after the procedure.

The primary outcome was the score for overall pain (over the course of the previous week) as measured on a scale of 0 to 10 (with 0 indicating no pain, 10 indicating the maximum imaginable pain, and 1.5 as the minimal clinically important difference).[23,24] Secondary outcomes included quality of life, as measured with the use of the Quality

of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO), a 41-item vertebral-fracture–specific and osteoporosis-specific questionnaire (in which scores range from 0 to 100, with lower scores indicating a better quality of life)[25]; the Assessment of Quality of Life (AQoL) questionnaire, a well-validated instrument that is sensitive to changes in the frail elderly (scores range from 0 to 1, with 1 indicating perfect health and 0.06 representing the minimal clinically important difference)[26]; and the European Quality of Life–5 Dimensions (EQ–5D) scale (scores range from 0 to 1, with 1 indicating perfect health and 0.074 representing the minimal clinically important difference).[27] Other secondary outcomes included the scores for pain at rest and pain in bed at night (on a scale of 0 to 10, with higher scores indicating more pain); and the score on a modified 23-item version of the Roland–Morris Disability Questionnaire (RDQ, in which scores range from 0 to 23, with higher numbers indicating worse physical functioning, and 2 to 3 points representing the minimal clinically important difference).[28]

Perceived recovery with respect to pain, fatigue, and overall health was measured on 7-point ordinal scales ranging from "a great deal worse" to "a great deal better." Responses of "moderately better" or "a great deal better" were classified as successful outcomes. Adverse events, including incident clinical fractures, were assessed at each time point with the use of open-ended questions.

STATISTICAL ANALYSIS

The primary end point was the score for overall pain at 3 months. We calculated that a sample of 24 participants per group would be required for the study to have 80% power to show at least a 2.5-unit advantage of vertebroplasty over placebo with respect to pain, with a standard deviation of 3.0, based on a two-sided type 1 error rate of 5%. Although a change of 1.5 units on a scale that ranges from 0 to 10 is regarded as the minimal clinically important difference with respect to pain,[24] published studies at the time the trial was designed showed that vertebroplasty conferred very large effects (e.g., more than 5 points on a 10-point scale). We also calculated that a sample of 82 participants per group would be needed to show an increase by a factor of three in the risk of further vertebral fractures at 24 months.[19] However, we terminated trial enrollment before reaching the sample size for long-term outcomes because it became evident that this sample size would not be achieved within an acceptable period of time and that the study's power was sufficient to address the primary aim. This decision was made without knowledge of any outcome results.

All analyses were performed according to the intention-to-treat principle. Baseline differences between the groups were assessed with the use of Student's t-test or nonparametric tests, as appropriate. Changes from baseline to 1 week, 1 month, 3 months, and 6 months in measures of pain and scores on the QUALEFFO, AQoL, RDQ, and EQ–5D were compared with the use of multiple linear regression analyses. Estimates of between-group mean differences adjusted for baseline values and the stratification variables are presented, together with 95% confidence intervals. All results are presented as improvements from baseline.

We compared measures of a perceived successful outcome (reports of feeling moderately better or a great deal better vs. no change or feeling worse) after vertebroplasty and after the sham procedure by calculating the relative risks at each time point, using log binomial regression.[29] We performed similar analyses among participants who reported a reduction in pain that was greater than 2.5 units. All reported P values are two-sided and have not been adjusted for multiple testing. Analyses were performed with the use of Stata software version 10.0 (StataCorp).

RESULTS

Of 468 potential participants, 78 met the inclusion criteria and were randomly assigned to a study group (38 to the vertebroplasty group and 40 to the placebo group). Figure 1 shows the number of participants involved in the trial from assessment for eligibility through the 6-month follow-up. Two participants in the vertebroplasty group and one in the placebo group died during the follow-up period for reasons thought to be unrelated to the trial. At the 6-month assessment, complete data were available for 71 of the 78 participants (91%).

The baseline characteristics of the participants were similar in the two groups (Table 1; additional information on baseline characteristics can

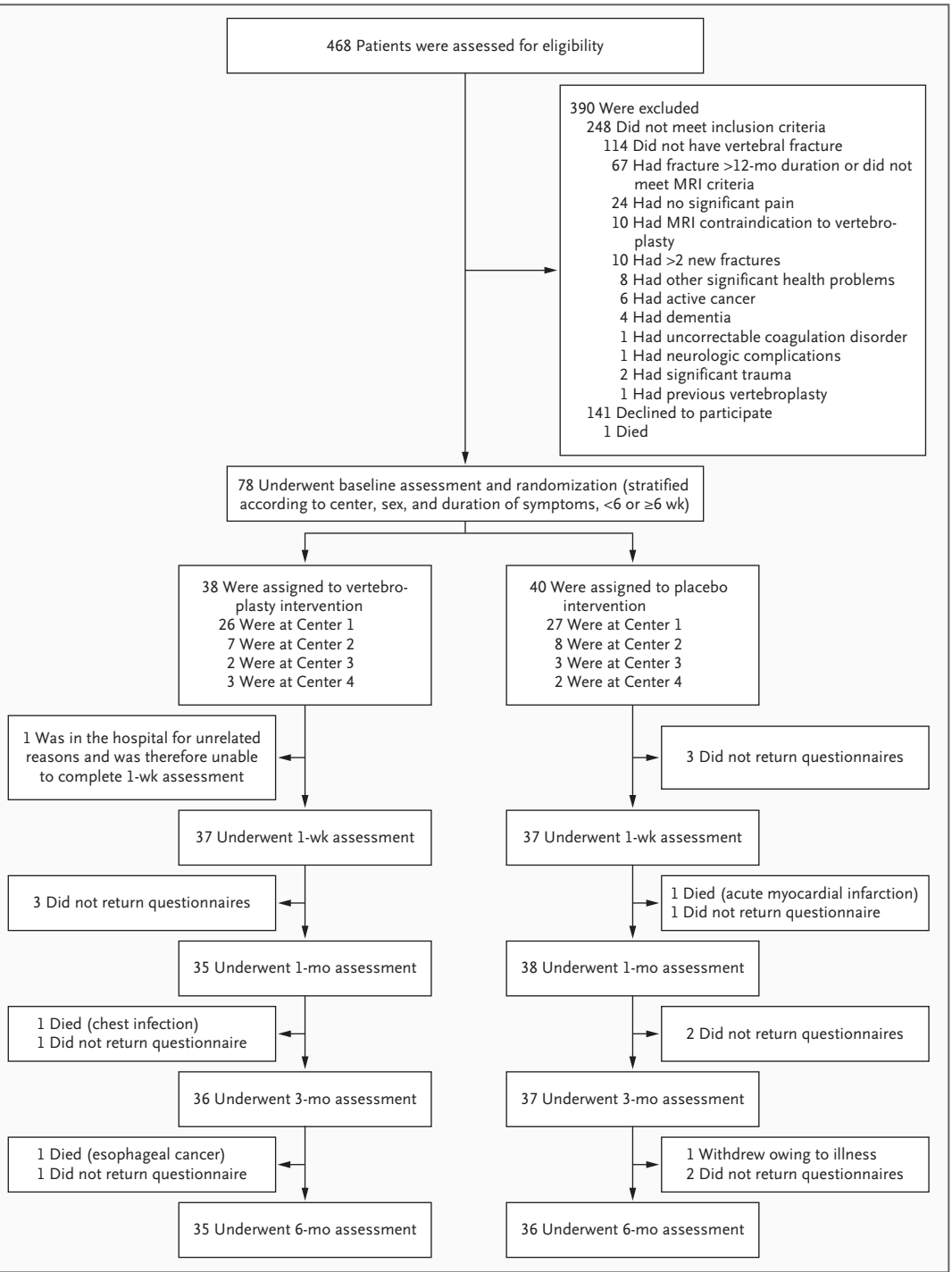

Figure 1. Enrollment, Assigned Intervention, and Follow-up.

Patients who did not complete one interim assessment either because they did not return a questionnaire or, in one case, because of hospitalization for a reason unrelated to the study could be included in subsequent assessments.

be found in Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). In most participants, one vertebral fracture was treated; seven participants in each group had a second vertebra treated. In the vertebroplasty group, the mean (±SD) volume of cement injected in the vertebrae was 2.8±1.2 ml. Minimal leakage was recorded in the case of 14 participants (37%).

No significant differences between groups were seen in the primary outcome of overall pain at 3 months. Mean reductions in the score for overall pain in the vertebroplasty and placebo groups were 2.6±2.9 and 1.9±3.3, respectively (adjusted between-group difference, 0.6; 95% confidence interval, −0.7 to 1.8) (Table 2 and Fig. 2). There were no significant between-group differences in any other outcomes, except for the total QUALEFFO score at 1 week, which favored the placebo group. Results for the subscales of the QUALEFFO, perceived successful outcome with respect to fatigue and overall health, and reports of more than a 2.5-unit reduction in pain scores are shown in Table 2 in the Supplementary Appendix.

The observed differences between groups were smaller than the minimal clinically important differences for all outcomes; the 95% confidence intervals indicated that the ranges of plausible differences between groups were unlikely to have included differences of any practical importance. The results of the unadjusted group comparisons

Table 1. Baseline Characteristics of the Study Participants.*

Characteristic	Vertebroplasty (N=38)	Placebo (N=40)
Age — yr	74.2±14.0	78.9±9.5
Female sex — no. (%)	31 (82)	31 (78)
Duration of back pain — wk		
Median	9.0	9.5
Interquartile range	3.8–13.0	3.0–17.0
Duration of symptoms <6 wk — no. (%)	12 (32)	13 (32)
Body-mass index†	25.6±5.5	24.6±5.7
Duration of corticosteroid use — yr‡		
Median	3.0	2.0
Interquartile range	0.3–10.8	0.3–12.5
Pain score§		
Overall	7.4±2.1	7.1±2.3
At rest	4.5±2.3	4.8±2.8
In bed at night	4.8±3.0	3.6±3.2
QUALEFFO total score¶	56.9±13.4	59.6±17.1
AQoL score‖	0.33±0.25	0.27±0.26
RDQ score**	17.3±2.8	17.3±2.9
EQ–5D score††	0.30±0.32	0.28±0.33
Timed Up and Go test — sec‡‡	20.5±8.8	23.9±13.8
Medication for osteoporosis — no. (%)		
Any	35 (92)	37 (92)
Calcium supplements	27 (71)	25 (62)
Vitamin D	14 (37)	18 (45)
Bisphosphonates	31 (82)	32 (80)
One or more previous vertebral fractures — no. (%)	18 (47)	21 (52)
Opioids for pain — no. (%)	30 (79)	34 (85)

Table 1. (Continued.)

Characteristic	Vertebroplasty (N = 38)	Placebo (N = 40)
T score for bone mineral density ≤2.5 — no./total no. (%)		
Lumbar	21/34 (62)	21/28 (75)
Femoral neck	13/34 (38)	15/28 (54)
Severity of fracture — no./total no. of fractures (%)§§		
Mild	13/45 (29)	12/47 (26)
Moderate	21/45 (47)	24/47 (51)
Severe	11/45 (24)	11/47 (23)
No. of vertebral bodies treated — no. (%)		
One	31 (82)	33 (82)
Two	7 (18)	7 (18)

* Plus–minus values are means ±SD. There were no significant differences between the groups for any of the measured variables.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The data are based on a total of 12 participants in the vertebroplasty group and 17 in the placebo group who reported using corticosteroids.
§ Pain was assessed on a scale of 0 to 10, with higher numbers indicating more pain and with 1.5 as the minimal clinically important difference.
¶ Scores on the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) range from 0 to 100, with higher scores indicating worse quality of life.
‖ Scores on the Assessment of Quality of Life (AQoL) range from –0.04 to 1.0, with 1 indicating perfect health and 0.06 representing the minimal clinically important difference.
** Scores on the Roland–Morris Disability Questionnaire (RDQ) range from 0 to 23, with higher scores indicating worse physical functioning and 2 to 3 points representing the minimal clinically important difference. Scores were available for 30 participants in the vertebroplasty group and 29 in the placebo group. This questionnaire was added to the protocol in June 2005 (to allow comparison with outcomes in another trial[30]).
†† Scores on the European Quality of Life–5 Dimensions (EQ–5D) questionnaire range from 0 to 1, with 1 indicating perfect health and 0.074 representing the minimal clinically important difference. Scores were available for 30 participants in the vertebroplasty group and 29 in the placebo group. This questionnaire was added to the protocol in June 2005 (to allow comparison with outcomes in another trial[30]).
‡‡ The Up and Go test measures the time required to rise from a standard arm chair, walk 3 m, turn around, return to the chair, and sit down again.[22] Results were available for 36 participants in the vertebroplasty group and 37 in the placebo group.
§§ The severity of the fracture was assessed according to the semiquantitative grading system of Genant et al.,[20] on a scale of 0 to 3, with higher numbers indicating greater vertebral collapse.

were qualitatively similar to the results of the adjusted comparisons (data not shown). Analysis with the use of a linear mixed-effect, repeated-measures model to assess the constancy of the effect of vertebroplasty at 1 week and at 1, 3, and 6 months also showed no significant differences between the groups over time (data not shown).

The results appeared to be consistent irrespective of the duration of symptoms (<6 weeks vs. ≥6 weeks, or as a continuous measure), sex, treatment center, or presence or absence of previous vertebral fractures (P>0.10 for all assessments of interactions). Use of opioids decreased over time, with no significant between-group differences: at 1 week, 10 participants (3 in the vertebroplasty group and 7 in the placebo group) had stopped taking opioids; at 1 month, 13 (4 in the vertebroplasty group and 9 in the placebo group) had stopped; at 3 months, 22 (11 in each group) had stopped; and at 6 months, 35 (17 in the vertebroplasty group and 18 in the placebo group) had stopped.

Seven participants (three in the vertebroplasty group and four in the placebo group) reported an incident clinical vertebral fracture within 6 months after the study intervention (Table 3). Three participants (one in the vertebroplasty group and two in the placebo group) reported new rib fractures at 1 week. One participant in the vertebroplasty group did not receive intravenous cephalothin owing to multiple drug allergies, and an adjacent new fracture and osteomyelitis developed, necessitating surgical drainage and antibiotic treatment

Table 2. Outcomes at 1 Week and at 1, 3, and 6 Months, According to Intervention Group.*

Outcome Measure	1 Week			1 Month		
	Change in Vertebroplasty Group	Change in Placebo Group	Adjusted Between-Group Mean Difference (95% CI)†	Change in Vertebroplasty Group	Change in Placebo Group	Adjusted Between-Group Mean Difference (95% CI)†
Pain score‡						
Overall	1.5±2.5	2.1±2.8	−0.7 (−1.8 to 0.4)	2.3±2.6	1.7±3.3	0.5 (−0.8 to 1.7)
At rest	0.8±3.0	1.3±3.9	−0.2 (−1.5 to 1.1)	1.4±2.9	1.2±4.0	0.5 (−0.9 to 1.8)
In bed at night	0.9±2.7	0.4±2.8	−0.1 (−1.3 to 1.1)	1.9±2.8	0.5±3.3	0.8 (−0.5 to 2.1)
QUALEFFO total score§	−0.5±7.4	3.6±9.2	−4.0 (−7.8 to −0.2)	2.8±9.3	2.4±12.3	0.9 (−4.2 to 6.0)
AQoL score¶	0.0±0.2	0.0±0.2	0.0 (−0.1 to 0.1)	0.0±0.2	0.1±0.3	0.0 (−0.1 to 0.1)
RDQ score‖	1.8±5.0	4.0±6.8	−2.1 (−5.2 to 0.9)	4.4±6.6	3.1±6.8	1.7 (−1.8 to 5.2)
EQ–5D score**	0.1±0.3	0.1±0.3	0.0 (−0.1 to 0.2)	0.1±0.3	0.1±0.3	0.0 (−0.1 to 0.1)
	Change in Vertebroplasty Group	Change in Placebo Group	Relative Risk (95% CI) ††	Change in Vertebroplasty Group	Change in Placebo Group	Relative Risk (95% CI)††
Perceived pain — no. (%)‡‡						
Better	6 (16)	13 (35)	0.5 (0.2 to 1.1)	12 (34)	9 (24)	1.5 (0.7 to 3.0)
No change	26 (70)	23 (62)		21 (60)	20 (53)	
Worse	5 (14)	1 (3)		2 (6)	9 (24)	

* Plus–minus values are means ±SD. Values were calculated on the basis of 37 participants in each group at 1 week; 35 in the vertebroplasty group and 38 in the placebo group at 1 month; 36 and 37 in the two groups, respectively, at 3 months; and 35 and 36 in the two groups, respectively, at 6 months. CI denotes confidence interval.

† The between-group difference was calculated with the use of multiple linear regression analyses adjusted for stratification variables and baseline values. Positive values favor the vertebroplasty group.

‡ Pain was assessed on a scale of 0 to 10, with higher numbers indicating more pain and with 1.5 as the minimal clinically important difference.

§ Scores on the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) range from 0 to 100, with higher scores indicating worse quality of life.

¶ Scores on the Assessment of Quality of Life (AQoL) questionnaire range from −0.04 to 1.0, with 1 indicating perfect health and 0.06 representing the minimal clinically important difference.

‖ Scores on the Roland–Morris Disability Questionnaire (RDQ) range from 0 to 23, with higher scores indicating worse physical functioning and 2 to 3 points representing the minimal clinically important difference. The values were calculated on the basis of 30 participants in the vertebroplasty group and 29 in the placebo group at each time point.

** Scores on the European Quality of Life–5 Dimensions (EQ–5D) questionnaire range from 0 to 1, with 1 indicating perfect health and 0.074 representing the minimal clinically important difference. The values were calculated on the basis of 30 participants in the vertebroplasty group and 29 in the placebo group at each time point.

†† The relative risk is for the comparison of "better" with "no change" or "worse" (with "better" defined a priori as being a successful outcome).

‡‡ Pain was classified as "better" if the participant indicated that the pain was moderately or a great deal better than before the intervention and as "worse" if the pain was reported to be moderately or a great deal worse than before the intervention.

approximately 2 weeks after randomization, but this participant recovered fully.

DISCUSSION

We found no beneficial effect of vertebroplasty over a sham procedure at 1 week or at 1, 3, or 6 months among patients with painful osteoporotic vertebral fractures. Overall scores on measures of pain improved modestly in both groups over time, as did scores for pain at rest and during the night, physical functioning, and quality of life, but there were no significant between-group differences.

The finding of the lack of an observed benefit of vertebroplasty at all time points up to and including 6 months is at odds with most, but not all, earlier reports. For example, one controlled be-

3 Months			6 Months		
Change in Vertebroplasty Group	Change in Placebo Group	Adjusted Between-Group Mean Difference (95% CI)†	Change in Vertebroplasty Group	Change in Placebo Group	Adjusted Between-Group Mean Difference (95% CI)†
2.6±2.9	1.9±3.3	0.6 (–0.7 to 1.8)	2.4±3.3	2.1±3.3	0.1 (–1.2 to 1.4)
1.4±3.4	1.5±3.7	0.1 (–1.1 to 1.4)	2.0±3.2	0.9±3.2	0.3 (–0.9 to 1.5)
1.6±2.9	0.8±3.4	0.2 (–0.9 to 1.3)	1.5±3.6	1.6±3.6	–0.2 (–1.6 to 1.1)
6.0±9.6	6.1±13.7	0.7 (–4.4 to 5.7)	6.4±13.4	6.1±13.4	0.6 (–5.1 to 6.2)
0.0±0.2	0.1±0.3	0.0 (–0.1 to 0.1)	0.0±0.3	0.1±0.3	0.1 (–0.1 to 0.2)
3.7±5.4	5.3±7.2	–1.5 (–4.8 to 1.7)	4.1±5.8	3.7±5.8	0.0 (–3.0 to 2.9)
0.2±0.3	0.2±0.4	0.0 (–0.1 to 0.2)	0.2±0.4	0.2±0.4	0.0 (–0.1 to 0.2)
Change in Vertebroplasty Group	Change in Placebo Group	Relative Risk (95% CI)††	Change in Vertebroplasty Group	Change in Placebo Group	Relative Risk (95% CI)††
14 (39)	12 (32)	1.2 (0.6–2.2)	16 (46)	15 (42)	1.1 (0.6 to 1.9)
19 (53)	18 (49)		12 (34)	16 (44)	
3 (8)	7 (19)		7 (20)	5 (14)	

fore–after study showed a difference favoring vertebroplasty at 24 hours, but at 6 weeks, 6 months, and 12 months, measures of pain and physical functioning after vertebroplasty were similar to those after conservative therapy.[8]

In contrast to previous studies, ours was a randomized trial that included a control group undergoing a sham procedure and that had a study design in which participants, investigators (other than the interventional radiologists), and outcome assessors were unaware of the intervention assignment and in which no crossover was permitted. The rate of attrition in our study was low (less than 10%).

It has been argued that performing a randomized, placebo-controlled trial of vertebroplasty is unnecessary and unethical in view of the published results of numerous studies that suggest a benefit of vertebroplasty.[31] Our results show — not for the first time[32,33] — the hazards of relying on the results of uncontrolled or poorly controlled studies to assess treatment efficacy. These studies tend to overestimate the treatment benefit by failing to take into account the favorable natural history of the condition, the tendency for a regression to the mean, and the placebo response to treatment, which may be amplified when the treatment is invasive.[10,34] Raised expectations of an invasive intervention may explain the effect of a sham procedure.[33]

It is unlikely that the negative results of our study were due to the inclusion of participants who were not likely to benefit from vertebroplasty. The participants were similar to those enrolled in previous controlled studies.[7-9,28] However, selection bias cannot be entirely ruled out, since 30% of potentially eligible participants declined to participate in the study. Vertebroplasty was not readily available when our trial commenced, but reimbursement approval granted in November 2005 prompted active promotion of the procedure.[35] Although our ability to assess potential effect modifiers was limited by the failure of the trial to show any overall benefit of vertebroplasty and by the study's relatively small sample size, we found no evidence that the duration of pain modified the effect of treatment, and only two participants in each group had had symptoms for longer than 6 months. Furthermore, consistent with previous controlled studies, all participants were required to have bone edema in the affected vertebrae on MRI, a finding that is reported to predict a ben-

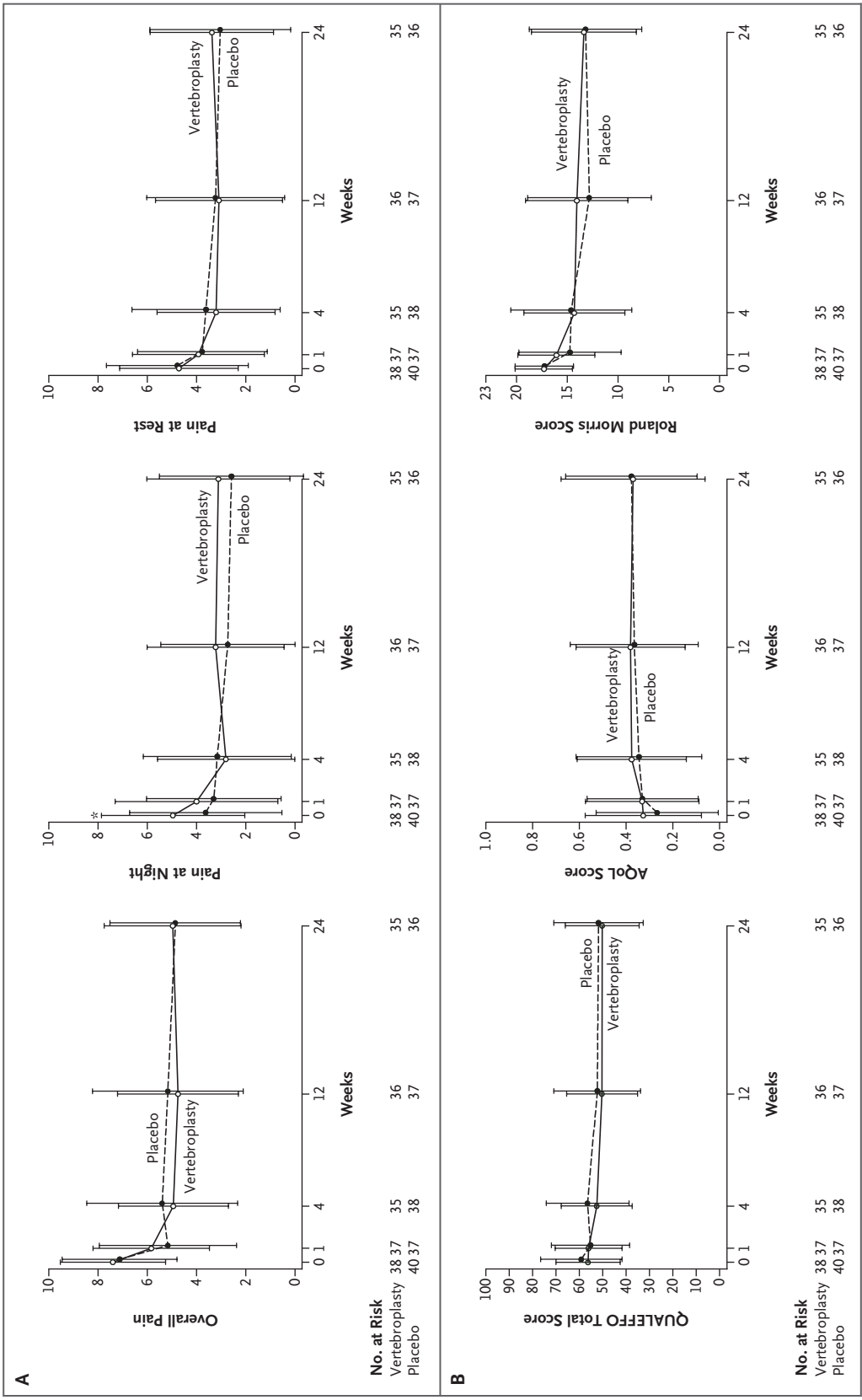

Figure 2. Scores on Measures of Overall Pain, Pain at Night and at Rest, Quality of Life Questionnaire of the European Foundation for Osteoporosis, Assessment of Quality of Life, and Modified Roland–Morris Disability Questionnaire, According to Time and Intervention Group.

Pain was assessed on a scale of 0 to 10, with higher numbers indicating more pain and with 1.5 as the minimal clinically important difference (Panel A). Scores on the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) range from 0 to 100, with higher scores indicating worse quality of life; scores on the Assessment of Quality of Life (AQoL) range from −0.04 to 1.0, with 1 indicating perfect health and 0.06 representing the minimal clinically important difference; scores on the Roland–Morris Disability Questionnaire (RDQ) range from 0 to 23, with higher scores indicating worse physical functioning and 2 to 3 points representing the minimal clinically important difference (Panel B). I bars indicate standard deviations.

Table 3. Number of Incident Clinical Fractures and Adverse Effects Reported at 1 Week and at 1, 3, and 6 Months.*

Event	Vertebroplasty					Placebo				
	1 wk	1 mo	3 mo	6 mo	Total	1 wk	1 mo	3 mo	6 mo	Total
Incident fracture										
Vertebra	1	1		1	3		3	1		4
Hip			1		1					
Rib	1		1		2	2			2	4
Pelvis							1			1
Osteomyelitis		1			1					
Tightness in the back or rib cage		1			1			2		2
Pain or burning in thigh or leg	3		1		4	1		1		2
Stomach pain	1			1	2			1		1
Increased pain or muscle cramping around puncture site	1		1		2				1	1
Chest pain	3				3					

* An incident clinical fracture was defined as a fracture that was found on investigation after a patient presented with pain.

eficial response to treatment.[21] Although a short but considerable learning curve for vertebroplasty has been described,[36] it is also unlikely that this explains our negative results; our trial involved experienced interventional radiologists who were using standardized procedures. A 2-year follow-up for vertebral fracture is planned, but a sample larger than that in our trial will be needed in order for the study to have adequate power to assess the effect of vertebroplasty on this outcome.

In conclusion, our trial showed no significant benefit of vertebroplasty over a sham procedure during 6 months of follow-up among patients with recent osteoporotic vertebral fractures. These findings call into question the use of vertebroplasty for such patients.

Supported by grants from the National Health and Medical Research Council of Australia (284354), Arthritis Australia, the Cabrini Education and Research Institute, and Cook Australia. Dr. Buchbinder is the recipient of a National Health and Medical Research Council Practitioner Fellowship, and Dr. Osborne is the recipient of a National Health and Medical Research Council Population Health Career Development Award.

Dr. Buchbinder reports receiving grant support from Cook Australia to perform this trial. No other potential conflict of interest relevant to this article was reported.

We thank Dr. David Connell, Ms. Lainie Wengier, Dr. James Burnes, Dr. Michelle Leech, Dr. Winston Chong, Dr. Stuart Lyon, and members of the radiology departments of Cabrini Hospital, Royal Melbourne Hospital, Monash Medical Centre, and the Alfred Hospital for their participation in the trial.

REFERENCES

1. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA 2009;301:513-21.
2. Melton LJ III, Thamer M, Ray NF, et al. Fractures attributable to osteoporosis: report from the National Osteoporosis Foundation. J Bone Miner Res 1997;12:16-23.
3. Jones G, White C, Nguyen T, Sambrook PN, Kelly PJ, Eisman JA. Prevalent vertebral deformities: relationship to bone mineral density and spinal osteophytosis in elderly men and women. Osteoporos Int 1996;6:233-9.
4. Kanis JA, Johnell O. The burden of osteoporosis. J Endocrinol Invest 1999;22:583-8.
5. Ploeg WT, Veldhuizen AG, The B, Sietsma MS. Percutaneous vertebroplasty as a treatment for osteoporotic vertebral compression fractures: a systematic review. Eur Spine J 2006;15:1749-58.
6. Jensen ME, McGraw JK, Cardella JF, Hirsch JA. Position statement on percutaneous vertebral augmentation: a consensus statement developed by the American Society of Interventional and Therapeutic Neuroradiology, Society of Interventional Radiology, American Association of Neurological Surgeons/Congress of Neurological Surgeons, and American Society of Spine Radiology. J Vasc Interv Radiol 2007;18:325-30.
7. Voormolen MH, Mali WP, Lohle PN, et al. Percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures: the VERTOS Study. AJNR Am J Neuroradiol 2007;28:555-60.
8. Diamond TH, Champion B, Clark WA. Management of acute osteoporotic vertebral fractures: a nonrandomized trial comparing percutaneous vertebroplasty with conservative therapy. Am J Med 2003;114:257-65.
9. Álvarez L, Alcarez M, Pérez-Higueras A, et al. Percutaneous vertebroplasty: functional improvement in patients with osteoporotic compression fractures. Spine 2006;31:1113-8.
10. Moerman DE, Jonas WB. Deconstruct-

ing the placebo effect and finding the meaning response. Ann Intern Med 2002; 136:471-6.
11. Wardlaw D, Cummings S, 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.
12. Hollingworth W, Jarvik JG. Evidence on the effectiveness and cost-effectiveness of vertebroplasty: a review of policy makers' responses. Acad Radiol 2006;13:550-5.
13. Minutes — 31st meeting, 24 August 2005, Brisbane. Canberra, Australia: Medical Services Advisory Committee, 2005. (Accessed July 13, 2009, at http://www.msac.gov.au/internet/msac/publishing.nsf/Content/A2554B1F91BB28C0CA2575AD0082FD92/$File/Minutes%2031st%20Meeting%2024Aug05.pdf.)
14. Gray DT, Hollingworth W, Onwudiwe N, Deyo RA, Jarvik JG. Thoracic and lumbar vertebroplasties performed in US Medicare enrollees, 2001-2005. JAMA 2007;298:1760-2. [Erratum, JAMA 2007;298:2370.]
15. Lad SP, Patil CG, Lad EM, Hayden MG, Boakye M. National trends in vertebral augmentation procedures for the treatment of vertebral compression fractures. Surg Neurol 2009;71:580-4.
16. He SC, Teng GJ, Deng G, et al. Repeat vertebroplasty for unrelieved pain at previously treated vertebral levels with osteoporotic vertebral compression fractures. Spine 2008;33:640-7.
17. Uebelhart B, Casez P, Rizzoli R, Louis-Simonet M. Prophylactic injection of methylmetacrylate in vertebrae located between two previously cemented levels does not prevent a subsequent compression fracture in a patient with bone fragility. Joint Bone Spine 2008;75:322-4.
18. Trout AT, Kallmes DF. Does vertebroplasty cause incident vertebral fractures? A review of available data. AJNR Am J Neuroradiol 2006;27:1397-403.
19. Buchbinder R, Osborne RH, Ebeling PR, et al. Efficacy and safety of vertebroplasty for treatment of painful osteoporotic spinal fractures: a randomised controlled trial [ACTRN012605000079640]. BMC Musculoskelet Disord 2008;9:156.
20. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8:1137-48.
21. Pham T, Azulay-Parrado J, Champsaur P, Chagnaud C, Legré V, Lafforgue P. "Occult" osteoporotic vertebral fractures: vertebral body fractures without radiologic collapse. Spine 2005;30:2430-5.
22. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991;39:142-8.
23. Huskisson EC. Measurement of pain. J Rheumatol 1982;9:768-9.
24. Grotle M, Brox JI, Vøllestad NK. Concurrent comparison of responsiveness in pain and functional status measurements used for patients with low back pain. Spine 2004;29:E492-E501.
25. 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). Osteoporos Int 1999;10:150-60.
26. Hawthorne G, Osborne R. Population norms and meaningful differences for the Assessment of Quality of Life (AQoL) measure. Aust N Z J Public Health 2005;29:136-42.
27. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res 2005;14:1523-32.
28. Trout AT, Kallmes DF, Gray LA, et al. Evaluation of vertebroplasty with a validated outcome measure: the Roland-Morris Disability Questionnaire. AJNR Am J Neuroradiol 2005;26:2652-7.
29. McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. Am J Epidemiol 2003;157:940-3.
30. Gray LA, Jarvik JG, Heagerty PJ, et al. INvestigational Vertebroplasty Efficacy and Safety Trial (INVEST): a randomized controlled trial of percutaneous vertebroplasty. BMC Musculoskelet Disord 2007;8:126.
31. Wagner AL. Vertebroplasty and the randomized study: where science and ethics collide. AJNR Am J Neuroradiol 2005; 26:1610-1.
32. Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2002;347:81-8.
33. Flum DR. Interpreting surgical trials with subjective outcomes: avoiding UnSPORTsmanlike conduct. JAMA 2006;296: 2483-5.
34. Jarvik JG, Deyo RA. Cementing the evidence: time for a randomized trial of vertebroplasty. AJNR Am J Neuroradiol 2000; 21:1373-4.
35. Buchbinder R, Osborne RH. Vertebroplasty: a promising but as yet unproven intervention for painful osteoporotic spinal fractures. Med J Aust 2006;185:351-2.
36. Watts NB. Is percutaneous vertebral augmentation (vertebroplasty) effective treatment for painful vertebral fractures? Am J Med 2003;114:326-8.