University of Alberta

Percutaneous vertebroplasty for osteoporotic vertebral compression fracture

by

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Abstract

Background: Current vertebroplasty practices significantly vary due to differences in perceived effectiveness and safety of this interventional approach.

Objectives: To assess the efficacy and safety of Percutaneous Vertebroplasty in relieving pain due to osteoporotic vertebral compression fracture.

Methods: We conducted a systematic review. Randomized controlled trials were included in the efficacy review. All reports of major adverse effects were included in the safety review. We also included reports of minor adverse effects from studies of 30 consecutive cases or more.

Results: Vertebroplasty had no advantage over conservative management in improving pain, disability and Health-Related Quality of Life (HR QOL), with the exception of HR-QOL at 1 month. Mortality and major adverse events following vertebroplasty are rarely reported.

Conclusion: Decision to perform Percutaneous Vertebroplasty should be based on criteria that include a clear definition of conservative therapy and its failure prior to proceeding with the procedure.

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Chapter 1: Introduction

Vertebral compression fracture

Vertebral compression fracture (VCF) is the most common type of fracture in patients with osteoporosis (1), and is usually defined as at least a 15-20% reduction in the height of vertebral body on spinal radiographs (2) VCF is a common cause of acute and chronic back pain as well as spinal deformity and disability in older populations. Osteoporosis, weakness of the postural muscles and kyphosis are contributing factors for VCF. Based on radiographic assessments in a survey, the age-standardized incidence of VCF was estimated 12.1 per 1000-person-years in women and 6.8 per 1000-person-years in men (3). The prevalence of having at least one radiographic VCF is as high as 39% in both men and women aged 65 years or over (4) and the prevalence in both sexes significantly increases with age (5). It is not clear why the prevalence of VCF is almost the same in both sexes while the incidence is higher in women. The higher mortality rate in women with VCF may explain this mismatch (6). In the United States 1.5 million osteoporosis-related fractures occur every year with the associated direct cost of more than $17 billion. About half of those fractures or 700,000 are osteoporotic VCF(7).

Approximately two-thirds of VCF cases are termed "asymptomatic" in that the individuals do not present for medical care of acute back pain at the time of the incident fracture. However these "asymptomatic" fractures could as well associated with substantial spinal deformity, functional limitation, pulmonary compromise, lower quality of life, greater acute care length of stay, increased risk of future fractures, and higher mortality rates (8;9).

The primary clinical feature of VCF is back pain ; however, physical dysfunction is frequently seen in terms of restricted spinal movement, and impaired pulmonary function. The reduced physical function, in turn, affects activities of daily living which may have more indirect effects on health-related quality of life such as loss of independence, social isolation, and impaired overall quality of life (10;11).

Percutaneous Vertebroplasty

Management options for treating painful osteoporotic VCF are limited. Depending on clinical circumstances, conservative management may include pharmacologic therapies - analgesia (narcotic and non-narcotic), calcitonin, and muscle relaxants; and non-pharmacologic pain interventions - bed rest, physical therapy and back braces (12). Hospitalization may be required for management of pain or disability. When conservative management fails to provide adequate pain relief, Percutaneous Vertebroplasty (PV) is an alternative interventional option. The minimum requirements for "failure of conservative management" have not been universally agreed upon and some centers now perform PV in acute cases immediately after the diagnosis of a painful osteoporotic VCF has been established.

PV was first reported in 1987 (13). Through a small skin incision, large calibre needles are inserted into the vertebral body, usually via a transpedicular route. Under imaging guidance, most often fluoroscopy, bone cement is then injected into the vertebral body (14).

The average cost of performing PV at one vertebral level in an outpatient setting is estimated $1,500 US Dollars (15) but this will vary significantly depending on the imaging modalities used before and after the procedure as well as the follow-up care plan.

Documented adverse events during or after the procedure include increase in back pain, inadvertent extension of cement material into vascular or adjacent structures, neurological complications including paraplegia, new vertebral compression fracture or other fractures e.g. rib fracture, osteolysis in the bone surrounding the injected material, adjacent arthritis, infection, pulmonary cement embolism (PCE) and death.

Vertebroplasty mechanism of effect

The mechanism of pain reduction with PV is not clearly understood and there are at least three possible mechanisms: 1) mechanical stabilization of the fractured bone, 2) thermal destruction of nerve endings due to the high temperature reached during polymerization of the injected cement, and 3) chemical destruction of the nerve endings due to the chemical composition of the cement.

Why it is important to conduct this research

In recent years, PV has been widely adopted in clinical practice based on reports of the striking effect it appears to have on immediate pain relief. Nevertheless, the lack of conclusive evidence to support the effectiveness and safety of this procedure beseech a systematic review and meta-analysis of the available evidence. Furthermore, in the absence of high quality data, the practice of PV is highly variable. The prime clinical indication of painful osteoporotic VCF with "failed conservative therapy" is a definition that is particularly open to individual interpretation. The goal of this systematic review is to synthesize the relevant data on efficacy and safety of PV used for the treatment of osteoporotic VCF.

Cochrane Collaboration

Professor Archibald Leman Cochrane (1909 - 1988) in his book, Effectiveness and Efficiency: Random Reflections on Health Services suggested "because resources would always be limited, they should be used to provide equitably those forms of health care which had been shown in properly designed evaluations to be effective" (16). He was influential in establishment of the Oxford Database of Perinatal Trials (17). In 1992, in recognition of professor Cochrane's work and dedication to evidence based medicine, the first Cochrane centre was established in Oxford, UK. The Cochrane Collaboration was founded a year later in 1993. Currently, there are 53 Cochrane Collaboration review groups across the world providing authors methodological and editorial support for Cochrane Systematic Reviews. This research work was conducted in collaboration with the Cochrane Musculoskeletal Review Group (http://musculoskeletal.cochrane.org).

Chapter 2: Materials and Methods

Objective

To assess the efficacy and safety of PV in providing pain relief, improving physical function and attaining a higher level of health-related quality of life for persons with osteoporotic VCF.

Criteria for considering studies for ***EFFICACY*** review

Randomized controlled trials (RCTs) of vertebroplasty were included. To be eligible for inclusion, the generation of the allocation sequence had to be truly random.

Criteria for considering studies for ***SAFETY*** review

In a parallel review, we focused on the adverse events. In addition to the RCTs, observational studies were included where the adverse event was a direct result of the vertebroplasty procedure e.g. pulmonary cement embolism (PCE). This approach is not recommended for assessment of adverse events in drugs but, in the case of vertebroplasty, certain adverse events could never have happened if the patient had not had vertebroplasty. New osteoporotic VCF weeks or months following the vertebroplasty procedure is an exception because incident fractures are common in all osteoporotic patients.

Reports on adverse events were divided to 2 main groups. The first group consisted of major adverse events - a) death, b) life threatening complication e.g. cardiac/pulmonary cement embolism or c) life altering event e.g. paraplegia. The second group consisted of all other adverse events directly related to PV such as vertebral cement leakage. For the first group, we included all study designs including case reports to ensure all reports of significant adverse events are captured. For the second group we included studies with or without a comparator group when data were available for at least 30 consecutive patients who underwent PV. This provided an estimate of frequency or at least the possibility of sorting adverse events from the most common to the least common.

Study participants

Only patients with osteoporotic VCF were included. The diagnosis of osteoporosis can be based on bone mineral densitometry or explicit clinical diagnostic criteria.

Study interventions

Options for treatment of osteoporotic VCF include: Conservative management, PV, balloon vertebroplasty (often called kyphoplasty) and complementary and alternative medicine approaches.

When the efficacy of PV was evaluated within a RCT, vertebroplasty intervention was compared to the conservative management/usual care or sham procedure. PV consisted of a percutaneous injection of bone cement (usually poly methylmethacrylate (PMMA)) or similar substances into a vertebral body under imaging guidance (excluding balloon vertebroplasty). Conservative management was considered in a wide spectrum from clinical observation only, to any combination

of medications, bracing, physical therapy and alternative medicine. Sham procedure (placebo) was considered as a comparator in RCTs where patients underwent an almost identical procedure as PV up to the point of PMMA injection.

Clinical outcome measures

Primary outcomes

The primary outcome for efficacy is pain. It is frequently measured by Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS). These tools are discussed in detail in the medical literature. A 10-millimeter change in pain on a 100-millimeter pain VAS and a 1-point change in an 11-point NRS are considered the minimum clinically significant difference for pain (18;19).

Secondary outcomes

Secondary outcomes included function and health-related quality of life (HRQL). The most commonly used disease-specific HRQL for osteoporotic VCF back pain include: the Roland-Morris Disability Questionnaire and the Osteoporosis Quality of Life (OQL and miniOQL). The most commonly used generic HRQL measures include the Short-Form (36) Health Survey and European Quality of Life with 5 Dimensions (EQ-5D). Disease-specific measures focus on patients with the same condition such as VCF and, by far, are the most commonly used HRQL measures. They are more responsive to change than a generic health measure yet may not evaluate all health domains that are directly and indirectly affected by VCF or treatments. Generic health measures provide a general view of health across a variety of conditions and measure several dimensions of health. The wide spectrum of health domains permits comparison of HRQL across a variety of patient

populations. HRQL scores can be used as baseline or norm-based estimates against which the efficacy, effectiveness or efficiency of PV may be evaluated.

Adverse events during or after the procedure included all reported symptomatic and asymptomatic events. The asymptomatic adverse events were reported based on the post-procedural imaging findings i.e. local cement leakages that were identified on follw-up CT scans. Adverse events included death, any problem requiring secondary surgical intervention such as removal of cement, pulmonary cement embolism (PCE), neurological complications such as paresthesia and paraplegia, infection, new VCF or other new fractures such as rib fractures during the procedure, increase in back pain and leakage of injected cement.

The evaluation periods of the assessment must include a baseline evaluation, at the time of PV or at the time of decision not to perform PV as well as follow-up evaluations at: 1 to 3 days, 1 to 2 weeks, 1 month, 3 months and 6 months.

Literature search methods for identification of studies

Electronic searches

The original search strategy was developed for MEDLINE. We later searched the following electronic databases up to the September 2010: MEDLINE, CINAHL, EMBASE, the Cochrane Library, the Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) [Appendix 1].

The search was not limited to language but it was limited to date of publication because “percutaneous vertebroplasty” was first reported in 1987 and the term "vertebroplasty" in older medical literature was occasionally used when referring to other specific surgical interventions.

Searching other resources

We also conducted hand searching in the grey literature and considered the reference lists from published literature reviews. We contacted experts in the field for identifying possible additional unpublished data. We used Reference Manager® (Professional Edition version 11) software for management of the retrieved records resulted from our search.

Selection of studies

The first stage of the review process consisted of completing a rapid review form in Microsoft Word® that only included each record's "title" and "abstract" and assigning one of 3 pre-defined categories to each record. This was done to avoid bias due to the consideration of journal title, institution or the country of origin. A sample record in the abstract selection form is presented in Appendix 2.

Two review authors independently reviewed abstracts and classified records into 3 categories. Category “A” included studies that possibly provided data on the efficacy and safety based on *a priori* set of criteria: 1. presence of human subjects, 2. presence of vertebroplasty procedure, and 3. presence of at least one efficacy outcome measure e.g. pain, function or HRQL. Category “B” included studies that possibly provided data on safety only with criteria similar to those in category

"A" but no need for the presence of efficacy outcome data. Category "C" included the rest of studies that were not eligible for category "A" or "B" and rejected. This broad initial selection criteria approach was needed to ensure that all possibly relevant reports were read in full-text and considered for systematic review. In case of doubt, reviewers were instructed to include the title in Category "A". We then entered the selection results of each individual review author in MS Excel to identify any possible discrepancy. The exact agreement rate at this stage of selection for 4,093 records was 95.2 %. Two reviewers reviewed the discrepancies and finalized their answers. We assessed the inter-rater agreement with Cohen's kappa statistics where 1 indicates perfect agreement and 0 agreement of no better than chance (20). The calculated Cohen's kappa statistics for abstract selections was 0.68 which represents substantial agreement.

Data extraction and management

Efficacy

In the second stage of the process we reviewed 169 full papers for selection of studies for efficacy. We were aware that few RCTs would be available but we wanted to capture the study characteristics and general information from the non-randomized studies i.e. study population, setting, sample size and outcomes. To facilitate this step we used a one-page general information form that is presented in Appendix 3.

We reviewed 169 full papers in 4 phases. Two review authors independently reviewed full papers for efficacy and completed 1-page general information forms. The data in general information forms were then entered into the Microsoft Excel® software for assessment of discrepancies and kept for later data summarization.

Applying *a priori* eligibility criteria and using a standardized screening form facilitated a standardized review. Discrepancies regarding inclusion/exclusion of a study were resolved through discussion and consensus. The two review authors were provided with the discrepancy results and they finalized their answers without a need for a third person. The extracted data in the screening phase included: a) type of the study, b) type of participants based on the aetiology of VCF, c) number of study participants with osteoporotic VCF, d) type of interventions, e) number of osteoporotic VCF patients with vertebroplasty, f) outcomes (i.e. pain, function or disability, health-related quality of life), g) outcome measures (i.e. VAS, NRS, Rolland-Moris Disability questionnaire, Short Form-36 items, Osteoporosis Quality of Life), and h) the follow-up period.

Safety

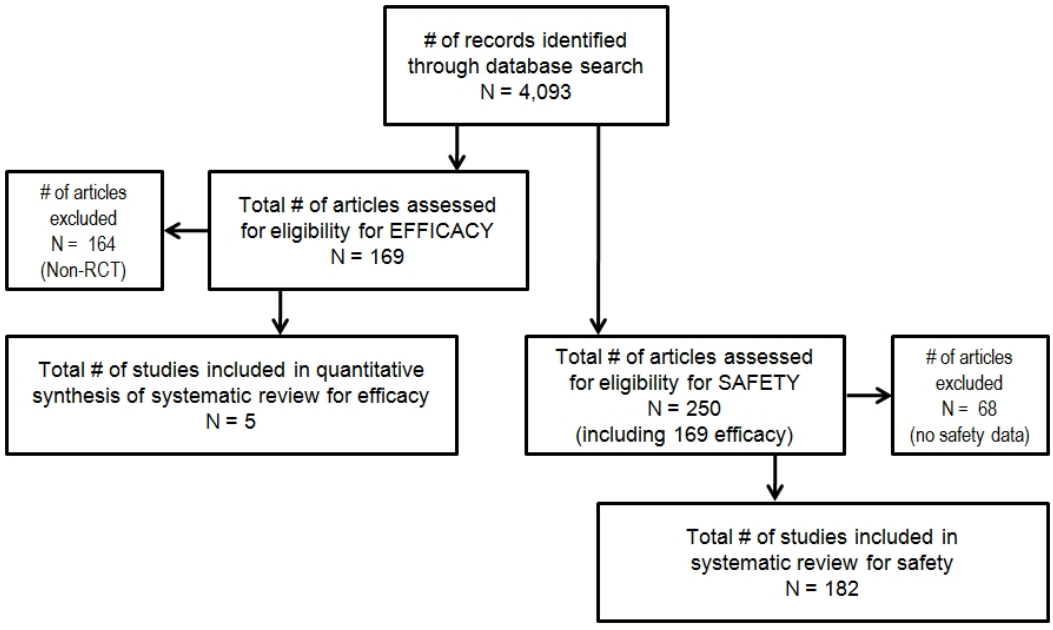
In the third stage of the process, we reviewed 250 full papers for reported adverse events. To facilitate this step we prepared a safety review data extraction form [Appendix 4].

We reviewed reports in 3 phases. Two review authors independently reviewed full papers for safety and completed forms. The data were then entered into the Microsoft Excel® software for assessment of discrepancies and later data summarization. The two review authors at each phase were provided with the discrepancy results and they finalized their answers without a need for a third person. These data were defined *a priori* and included: a) type of the study, b) type of participants based on the aetiology of VCF, c) number of study participants with osteoporotic VCF, d) type of interventions, e) number of osteoporotic VCF patients with vertebroplasty, f) count of adverse events with their timing such as: death, pulmonary cement embolism, new VCF, infection, any complication requiring surgery, increase in back pain, pulmonary distress, neurological

complications, other fractures e.g. rib fracture during PV, g) the total number of vertebral levels underwent vertebroplasty and h) any additional relevant information at the end.

The result of our search, review of the abstracts and review of full papers is presented in a search result flow diagram in Figure 1.

Figure 1. Flow diagram of study selection



Data extraction

After the above mentioned preliminary step there were 5 Randomized Controlled Trials that qualified for the systematic review meta-analysis.

Two review authors independently reviewed 5 RCTs. Data were compared for any discrepancies and then reviewed with both authors for resolving the discrepancies. We used extensive forms designed in Microsoft Word® at this time to capture study characteristics [Appendix 5] as well as the information regarding the Risk of Bias [Appendix 6]. For the results extraction we used Microsoft Excel®. Data for dichotomous and continuous outcomes were recorded at each time point for each group.

Study characteristics form included the following information:

- General information: publication year, title, author names, address, source of funding, setting, country
- Methods: number of study and comparison groups, design, inclusion criteria, exclusion criteria, blinding, randomization, analysis methods
- Study participants: baseline characteristics for both the intervention and sham/control groups, duration of disease, time from diagnosis, co-morbidities, medications allowed or withdrawn
- Trial outcomes: primary, secondary, adverse events

Assessment of risk of bias in included studies

For assessment of risk of bias of the included studies, the following aspects for each individual trial were assessed:

- Adequacy of the sequence generation: a random component in the study described for sequence generation process such as random number table, random number generator
- Allocation concealment: participants and investigators who were enrolling the participants could not foresee assignment
- Blinding: blinding of participants and the key study personnel ensured or the outcome measurements are not likely to be influenced by lack of blinding
- Addressing incomplete outcome data: no missing outcome data or reasons for missing outcome data unlikely to be related to the true outcome or balanced missing data across study groups
- Free of selective reporting: availability of the study protocol and reporting on all pre-specified outcomes
- Free of other bias: when the study appears to be free of other sources of bias
- Criteria for each of these areas were evaluated using a 3-point scale: YES (low risk of bias), NO (high risk of bias), and UNCLEAR (lack of information or certainty).

Measures of treatment effect

When data were sufficiently homogenous we performed a meta-analysis. We used the Mean Difference (MD) approach for continuous data unless the scales used for measuring the same

outcome were somewhat different in which case we used the Standardized Mean Difference (SMD). We analyzed the extracted data in Review Manager® (version 5.0.25) (21).

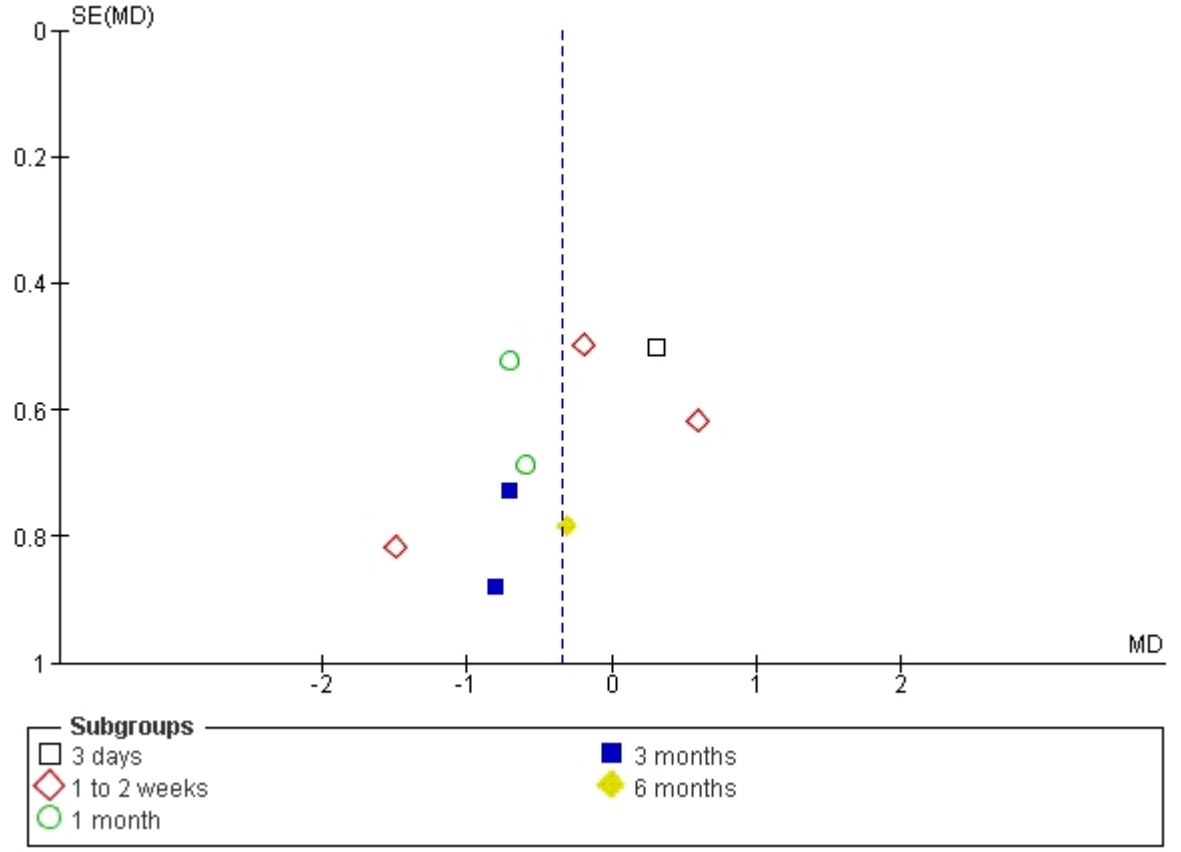
Assessment of heterogeneity

We conducted a test for heterogeneity of the data at baseline using the Chi^2 with a P value of less than 0.10 and the I^2 statistics of more than 50% as an indication of significant heterogeneity.

Assessment of reporting biases

A funnel plot was graphically depicted to explore the potential publication bias (Figure 2). It should be noted that there were only 4 RCTs available. It is recommended to treat the results of a meta-analysis with caution when there are only few RCTs available (22).

Figure 2. The funnel plot of effect estimate for pain against standard error in the 4 RCTs reporting pain at 3 days, 1 to 2 weeks, 1 month, 3 months, and 6 months.



MD = Mean difference
SE (MD) = Standard Error of the Mean Difference

Data synthesis

We determined that a random-effects model should be used in the meta-analysis because despite the diagnosis of osteoporotic VCF in all patients who enrolled in the RCTs, duration and severity of osteoporosis as well as the presence of co-morbidities were not clear (heterogeneity) and it was

assumed that the underlying effects follow a normal distribution. The results were assessed at 1 to 2 weeks, 1 month, 3 months, and 6 months.

Sensitivity analysis

To explore the differences in the effect size in terms of the effect of blinding, we divided studies into 2 groups. In the first group, blinding of patients was achieved by a sham procedure (23;24). In the second group patients were aware of the treatment approach (25-27).

Chapter 3: Results

Description of studies

The search results flow diagram is presented in Figure 1. We have included the details about each included RCT in Appendix 7: Characteristics of included studies.

Electronic databases were searched in 4 phases in 2007, 2008, 2009, and 2010 for the period of January 1987 to September 2010. The results of the multiple searches were merged in the Reference Manager with a total number of 4,093 records. After removing duplicate reports, the titles and abstracts of all records were evaluated to determine eligibility for full paper review identifying 169 studies for further assessment for efficacy and 250 studies for safety. We retrieved full text papers and recorded information in data collection sheets for all studies. Finally, only 5 publications of RCT met the inclusion criteria for complete efficacy review (23-27). For two RCTs the Standard Deviations (SD) were not provided in the original report which we received after correspondence with the principle investigators (25;27). For the safety review, we included 182 papers that provided relevant safety data (Table 1).

Table 1. Included studies after full-paper review for safety

(28) Afzal 2007
(29) Ahn 2008
(30) Al-Nakshabandi 2008
(31) Alvarez 2006
(32) Amar 2001
(33) Amoretti 2007
(34) Anselmetti 2008
(35) Anselmetti 2009
(36) Appel 2004
(37) Aslam 2008
(38) Barbero 2008
(39) Barr 2000
(40) Baumann 2006
(41) Bhatia 2006
(42) Birkenmaier 2007
(43) Bouvresse 2006
(44) Braiteh 2009
(45) Brown 2004
(46) Brown 2005
(23) Buchbinder 2009
(47) Carlier 2004
(48) Caudana 2008
(49) Caynak 2009
(50) Chang 2006
(51) Chen 2005
(52) Chen 2006
(53) Cheung 2006
(54) Chung 2006
(55) Cohen 2004
(56) Cosar 2009
(57) Cyteval 1999
(58) De Negri 2007
(59) Diamond 2003
(60) Diamond 2006
(61) Diel 2009
(62) Do 2005
(63) Docampo 2009
(64) Doo 2008
(65) Ehteshami 2010
(66) Evans 2003
(67) Fessl 2005
(68) Figueiredo 2009
(69) Francois 2003
(70) Frankel 2007
(71) Freitag 2006
(72) Gailloud 2005
(73) Gangi 2003
(74) Gaughen 2002a
(75) Gaye 2008
(76) Grados 2000
(77) Gray 2009
(78) Grohs 2005
(79) Ha 2006
(80) Han 2005
(81) Harrington 2001
(82) He 2008
(83) Heini 2000
(84) Hierholzer 2008
(85) Hochegger 2005
(86) Hodler 2003
(87) Jensen 1997
(88) Jung 2006
(89) Kallmes 2002
(24) Kallmes 2009
(90) Kao 2008
(91) Kaso 2008
(92) Kaufmann 2006
(93) Kawanishi 2006
(94) Kelekis 2003
(95) Kim 2004
(96) Kim 2005
(97) Kim 2005a
(98) Kim 2005b
(25) Klazen 2010
(99) Knavel 2009
(100) Ko 2009
(101) Kobayashi 2005
(102) Koch 2007
(103) Koh 2007
(104) Komemushi 2006
(105) Krauss 2006
(7) Kumar 2005
(106) Kumar 2010
(107) Layton 2007
(108) Lee 2004
(109) Lee 2006
(110) Lee 2008
(111) Legroux-Gerot 2004
(112) Li 2007
(113) Li 2008
(114) Liang 2006
(115) Liliang 2007
(116) Lin 2004
(117) Lin 2008
(118) Lin 2009
(119)lo Lo 2008
(120) Lopes 2004
(121) Lovi 2009
(122) Maehara 2006
(123) Martin 1999
(124) Masala 2008
(125) Masala 2009
(126) Masala 2009a
(127) McDonald 2009
(128) McGraw 2002
(129) McKiernan 2004
(130) McKiernan 2005
(131) Mirovsky 2006
(132) Monticelli 2005
(133) Muijs 2009
(134) Mummaneni 2006
(135) Muto 2005
(136) Nakano 2002
(137) Nakano 2006
(138) Nirala 2003
(139) Patel 2007
(140) Pedicelli 2009
(141) Peh 2002
(142) Perez-Higueras 2002
(143) Pitton 2004
(144) Pitton 2009
(145) Prather 2006
(146) Purkayastha 2005
(147) Quesada 2006
(148) Rapan 2009
(149) Righini 2006
(150) Rollinghoff 2009
(26) Rousing 2009
(151) Ryu 2002
(152) Sabuncuoglu 2008
(153) Schmid 2005
(154) Schmidt 2005
(155) Schofer 2009
(156) Seo 2005
(157) Sesay 2002
(158) Shapiro 2003
(159) Shin 2009
(160) Singh 2006
(161) Sonmez 2010
(162) Soyuncu 2006
(163) Sugimoto 2008
(164) Syed 2005
(165) Syed 2005a
(166) Syed 2006
(167) Syed 2006a
(168) Tanigawa 2006a
(169) Tanigawa 2007
(170) Tanigawa 2009
(171) Teng 2005
(172) Teng 2006
(173) Trout 2005a
(174) Trout 2006a
(175) Trout 2006b
(176) Tsai 2003
(177) Tsai 2010
(178) Tseng 2009
(179) Tsou 2002
(180) Uppin 2003
(181) Vasconcelos 2002
(182) Vats 2006
(183) Vcelak 2009
(184) Vogl 2006
(185) Voormolen 2003
(186) Voormolen 2006
(187) Voormolen 2006a
(188) Voormolen 2006b
(189) Voormolen 2006c
(27) Voormolen 2007
(190) Wagner 2006
(191) Weber 2006
(192) Wiggins 2007
(193) Winking 2003
(194) Winking 2004
(195) Wu 2007
(196) Wu 2010
(197) Yang 2008
(198) Yeom 2003
(199) Yu 2004
(200) Yu 2004a
(201) Zaccheo 2008
(202) Zeng 2006
(203) Zoarski 2002

Reference numbers are presented in the parenthesis

Included studies

Although all included studies were randomized, only 2 studies achieved the double-blinding with application of a sham procedure to patients in the control group (23;24). The intervention to control ratio was almost 1:1 in all 5 RCTs, however the follow-up periods significantly varied among the included studies. Buchbinder 2009 had 38 patients in the intervention and 40 in the control group and patients were assessed at baseline, 1 week, 1 month, 3 months, and 6 months time (23). Kallmes 2009 had 68 patients in the intervention and 63 in the control group and patients were assessed at baseline, 3 days, 2 weeks, and 1 month time (24). Klazen 2010 had 101 patients in the intervention and 101 in the control group and patients were assessed at baseline, 1 day, 1 week, 1 month, 3 months, 6 months and 12 months time (25). Rousing 2009 had 26 patients in the intervention and 24 in the control group and patients were assessed at baseline, and 3 months time (26). Voormolen 2007 had 18 patients in the intervention and 16 in the control group and patients were assessed at baseline, and 2 weeks time (27).

Sample size

The sample sizes were 78 in Buchbinder 2009, 131 in Kallmes 2009, 202 in Klazen 2010, 50 in Rousing 2009, and 34 in Voormolen 2007.

Setting

Buchbinder 2009 recruited patients referred from general practitioners and specialists as well as 4 hospital sites where patients were recruited from hospital inpatients and the emergency department from April 2004 to October 2008 (Australia). Kallmes 2009 reported that they were a multi-site

study where sites were selected on the basis of having: A) an established vertebroplasty practice for osteoporotic fractures, B) an enthusiastic local principal investigator, and C) an available research coordinator, and recruited patients from June 2004 to August 2008 (USA). Klazen 2010 recruited patients at the radiology departments of five large teaching hospitals in the Netherlands and one in Belgium from October 1, 2005 to June 30, 2008. Rousing 2009 study was conducted on 1 site (Spine Section, Department of Orthopaedics, University Hospital of Odense, Denmark). The study was conducted from January 2001 to January 2008 and midway through the study in November 2004, more outcomes were added as part of a PhD study. Voormolen 2007 recruited patients from 3 hospitals from July 2003 to June 2005 (Netherlands).

Participants

There were 495 patients from 5 RCTs included in the analysis; 251 were randomized to PV and 244 to control. The majority of patients were female (75%). The average age of participants was 75 years with a range of 50 to 96 years. In general, the inclusion criteria in all 5 RCTs required the presence of painful osteoporotic VCF. Details about the participants of each RCT are presented in Appendix 7: Characteristics of included studies.

Buchbinder 2009 included patients with back pain duration of no more than 12 months, one or two recent vertebral fractures, defined as vertebral collapse of grade 1 or higher according to the Genant grading system in which vertebral collapse is graded on a scale of 0 to 3, with higher numbers indicating greater vertebral collapse (204). Mean age was 74.2 (SD = 14.0) in the PV group and 78.9 (SD = 9.5) in the control group. Median duration of symptoms was 9 weeks in the PV group and 9.5 weeks in the control group. The prevalence of use of opioid medications for pain was 79% in the PV group and 85% in the control group.

Kallmes 2009 included patients with age of 50 years or older, a diagnosis of one to three painful osteoporotic VCF within the previous 12 months, and inadequate pain relief with standard medical therapy. Mean age was 73.4 in the PV group (SD = 9.4) and 74.3 (SD = 9.6) in the control group. The average Charlson co-morbidity index was about 2 in both groups. Mean duration of symptoms was 16 weeks in the PV and 20 weeks in the control group. There was no mention of earlier treatments for pain.

Klazen 2010 included patients aged 50 years or older with vertebral compression fracture on spine radiograph (minimum 15% height loss), fracture at the 5th Thoracic vertebral level or lower, back pain for 6 weeks or less; VAS score of 5 or more; bone oedema of vertebral fracture on MRI, focal tenderness at fracture level, as assessed by an internist on physical examination, and decreased bone density (T scores ≤–1).

Rousing 2009 included patients with intractable pain due to either acute (<2 weeks, 40 patients) or subacute (between 2 and 8 weeks, 10 patients) osteoporotic VCF. Mean age was 80 (95% CI of 76.9 to 83.2) in the PV group and 80 (95% CI of 77.6 to 82.6) in the control group. Mean duration of symptoms was 8.4 days (95% CI of 3.8 to 13) in PV group and 6.7 days (95% CI of 2.1 to 11.4) in the control group. There was also a significant difference in pain at baseline (7.5 in PV and 8.8 in control on 0-10 pain rating scale).

Voormolen 2007 included patients with VCF and height loss of the vertebral body (minimum15%) on x-ray of the spine, debilitating back pain related to the VCF refractive to medical therapy for at least 6 weeks and no longer than 6 months. Mean age was 73 in the PV group and 72 in the control group. Mean duration of symptoms was 85 days in the PV group and 76 days in the control group. The prevalence of use of opioid medications for pain was 33% in the PV group and 31% in the control group.

Intervention

The intervention of PV was compared to either a sham procedure (23;24) or standard treatment (25-27). Details of interventions in each RCT are presented in Appendix 7: Characteristics of excluded studies.

In Buchbinder 2009, patients were blinded for the assigned treatment. For PV approximately 3 ml. of bone cement was injected through the left pedicle to the affected vertebral body until satisfactory filling achieved on anterior, posterior and lateral images. When filling was not satisfactory, bi-pedicular approach was used. A sham procedure was performed in the control group where the same procedures as those in the PV group was performed up to the insertion of the needle into the bone. To simulate PV, the vertebral body was gently tapped with a blunt stylet, and bone cement was prepared to permeate the strong smell of the PMMA in the room. After the intervention, all trial participants continued to receive pain medications as needed as well as osteoporosis treatments according to the up-to-date guidelines. All procedures were performed by experienced interventional radiologists with appropriate certification to perform PV and adherence to standardized protocol.

In Kallmes 2009, patients were blinded for the assigned treatment. For PV, patients received conscious sedation and bone cement injected into the affected vertebral body through the vertebral pedicles using fluoroscopic guidance. In the control group methacrylate monomer was opened to simulate the bone cement odour but the needle was not placed into the vertebral body and bone cement was not injected. After the procedure, both groups were monitored for 1 to 2 hours before discharge. The PV and sham procedure was performed by experienced practitioners having performed a mean of approximately 250 PV procedures (ranging 50 to 800).

In Klazen 2010, patients were not blinded to the assigned treatment. PV patients underwent the Pre-procedural work-up (ECG, chest X ray, and blood sampling). Intravenous Cefazolin (2 g.) was administered 1 hour prior to the procedure. PV was performed under the fluoroscopic guidance on a single or biplane angiography system. After local infiltration of analgesics, two 11 or 13 gauge bone-biopsy needles were placed transpedicularly in the fractured vertebral body and bone cement was injected through bone-biopsy needles under continuous fluoroscopic monitoring to identify local cement leakage or migration into the venous system towards the lungs. When necessary, additional analgesia was used at the discretion of the treating physician. In patients who had more than one fracture with bone oedema on MRI, all vertebral bodies were treated in one or more procedures. After the procedure, a CT scan of the treated vertebral bodies was done with 2 mm slices to identify cement leakage outside the vertebral body or other possible local complications.

In Rousing 2009, patients were not blinded to the assigned treatment. PV was performed by orthopaedic surgeons specializing in spine surgery. Under mild conscious sedation, bone cement was injected into the affected vertebral bodies with a uni- or bi-pedicular approach. Both PV and the control group continued on pain medications and physical therapy as needed until discharge. Patients in the control group were offered brace treatment.

In Voormolen 2007, patients were not blinded to the assigned treatment. Patients were treated within 1 week of inclusion in the trial. PV was performed under local anesthesia with use of mono- or bi-plane fluoroscopy. In most cases of PV a bi-pedicular approach was taken for injection of the bone cement into the affected vertebral bodies. After PV a CT scan was performed to assess the injected levels and possible leakages. Pain medication continued on all patients based on the individual need.

Outcomes

In all trials the primary outcome measure was pain.

In Buchbinder 2009, the primary outcome was the score for overall pain over the course of the previous week. Scores for pain at rest and pain in bed at night (on a scale of 0 to 10, with higher scores indicating more pain. 10 indicating the maximum imaginable pain, and 1.5 as the minimal clinically important difference). The secondary outcomes were health-related quality of life on 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), utility on AQoL, disability on modified Roland-Morris Disability Questionnaire (RDQ) (disease-specific/ modified 23-item version), health-related quality of life on European Quality of Life-5 Dimensions (EQ-5D). Outcomes were reported at 1 wk, 1, 3, & 6 months.

In Kallmes 2009, the primary outcomes were disability on modified Roland-Morris Disability Questionnaire (RDQ) and patients' ratings of average back-pain intensity during the preceding 24 hours (on a scale of 0 to 10, with higher scores indicating more severe pain). The secondary outcomes were Pain Frequency Index and the Pain Bothersomeness Index, activities of daily living on Study of Osteoporotic Fractures-Activities of Daily Living (SOF-ADL) scale, HR QOL on European Quality of Life-5 Dimensions (EQ-5D) scale, use of opioid medications, Physical Component Summary (PCS) and Mental Component Summary (MCS) sub scales of Medical Outcomes Study 36-Item Short- Form General Health Survey (SF-36), version 2. Outcomes were reported at 1 month for the primary outcomes and 3, 14, and 90 days for the secondary outcomes.

In Klazen 2010, the primary outcomes were pain on VAS score and number of pain-free days (defined as days with a VAS score of 3 or lower). The secondary outcomes were cost-effectiveness (defined cost effectiveness as the ratio of difference in costs and difference in QALYs and the

difference in pain-free days), medical costs that was indexed to 2008 (web appendix) and derived from hospital billing systems and costing guidelines issued by the Dutch health insurance board, time without burdensome pain, and quality adjusted survival time, Quality-adjusted life-years (QALYs) were estimated with the EuroQol-5 dimensions (EQ-5D), the uncertainty with respect to the incremental cost-effectiveness ratio was assessed using the bootstrapping method. The tertiary outcomes: Quality of life measured with the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) a disease-specific questionnaire for osteoporosis, physical function with the Roland Morris Disability (RMD) questionnaire including additional questions about pain treatment, hospital stay, outpatient visits, and medical aids. Outcomes were reported at 1 month and 1 year.

In Rousing 2009, the primary outcomes were pain (VAS, Dallas Pain Questionnaire) and overall health (SF-36). The secondary outcomes were part of a PhD-study that was affiliated to the study and considered midway trough the study. Secondary outcomes included HR QOL measured on EuroQol (EQ5D), daily function (feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfers, mobility, and stairs) on Barthel index, cognitive status on modified mini-mental status examination (MMSE), and immediate balance on 3 physical tests (Timed Up & Go, tandem walking, "repeated chair stand"). Outcomes were reported at baseline and 3 months.

In Voormolen 2007, the primary outcome was pain on VAS. The secondary outcomes included type of analgesic use (ordinal variable from 0 (no analgesic use) to 3 (use of opiate derivatives), disability on the Roland-Morris Disability Questionnaire (RDQ), and HR QOL on QUALEFFO (QUALity of life questionnaire of the European Foundation For Osteoporosis). Outcomes were reported at 2 weeks.

Funding

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Excluded studies

Part I: Efficacy

After reviewing the full paper of 169 studies and collection of general information in data entry forms; we excluded 164 studies because treatment allocations were not truly random. Among these non-randomized studies there were 3 studies in which the results of vertebroplasty in patients with osteoporotic VCF were compared to a control group (31;60;137). According to our review protocol the initial plan was to include these studies in the synthesis using the methods for meta-analysis of non-randomized trials. But when new RCTs became available we excluded these 3 non-randomized studies from the meta-analysis and summarized their findings in Table 2.

Table 2. Summary of results from 3 non-randomized studies

Study (Reference)		Alvarez 2006 (31)		Diamond 2006 (60)		Nakano 2006 (137)	
Group		Vertebroplasty	Control	Vertebroplasty	Control	Vertebroplasty	Control
N		101	27	88	38	30	30
Age Mean & SD)		73.3 (7.9)	69.7 (7.7)	76.8 (8.7)	76.1 (10.0)	77 (7)	77 (8.2)
Male		20	5	32	7	8	8
Female		81	22	56	31	22	22
Pain Scale		0-10	0-10	0-25	0-25	0-10	0-10
Mean Pain on VAS (SD)	Baseline	8.76 (1.4)	7.3 (1.5)	20 (4)	20 (5)	7.93 (1.2)	7.47 (1.8)
	24 Hours	4.03 (2.2)	NA	8 (4)	19 (5)	NA	NA
	6 Weeks	NA	NA	5 (4)	7 (5)	NA	NA
	3 months	3.34 (2.3)	5.59 (1.7)	NA	NA	NA	NA
	6-12 months	3.06 (2.2)	4.52 (2.5)	3 (4)	4 (5)	0.70 (1.2)	2.57 (1.7)
	12 months	2.83 (1.9)	3.32 (1.7)	NA	NA	0.67 (1.1)	1.97 (1.3)
	24 months	NA	NA	2 (3)	3 (3)	NA	NA

N = Number of patients at each group of the study
VAS = Visual Analogue Scale
SD = Standard Deviation

Part II: Safety

We considered all 250 studies for full-paper safety review and collected information on data entry forms. After assessment of the collected information, we excluded 68 studies mainly due to the lack of any relevant safety information (Table 3).

Table 3. Excluded studies after full-paper review for safety

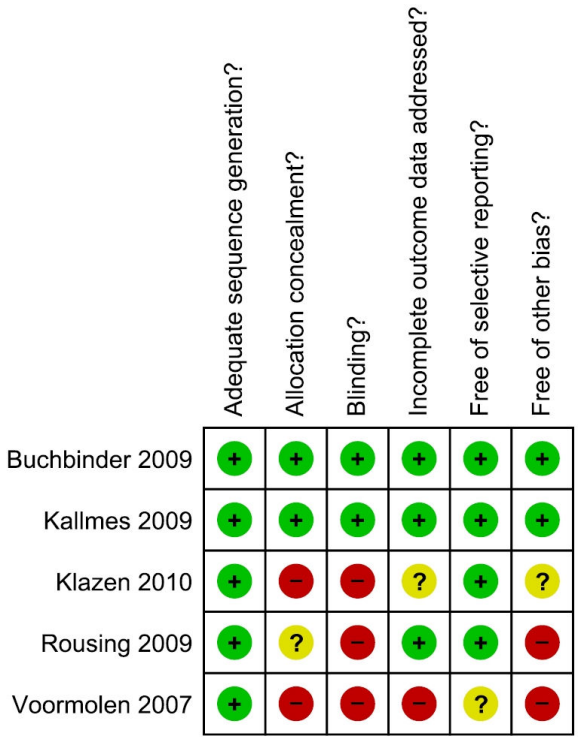
(205) Alfonso 2006	(223) Gibson 2006	(241) Komemushi 2005a	(259) Rad 2008
(206) Anselmetti 2005	(224) Grohs 2004	(242) Komemushi 2008	(260) Sadat-Ali 2008
(207) Benz 2009	(225) Hadjipavlou 2005	(243) Koyama 2005	(261) Serra 2007
(208) Brook 2008	(226) Harstall 2005	(244) Kruger 2003	(262) Singh 2006a
(209) Buchbinder 2006	(227) Heini 2004	(245) Lane 2002	(263) Tanigawa 2006
(210) Buchbinder 2008	(228) Hierholzer 2002	(246) Laredo 2004	(264) Teng 2003
(211) Chin 2006	(229) Hierholzer 2005	(247) Lehman 2008	(265) Togawa 2005
(212) Cortet 1999	(230) Hiwatashi 2007	(248) Liu 2010	(266) Trout 2005
(213) Costa 2009	(231) Hiwatashi 2007a	(249) Mannes 2006	(267) Trout 2006
(214) Deramond 1999	(232) Huntoon 2008	(250) Manzini 2007	(268) Trumm 2006
(215) Dublin 2005	(233) Jonsson 2006	(251) Martinez-Quinones 2003	(269) Walz 2006
(216) Emde 2003	(234) Kallmes 2003	(252) Masala 2005	(270) Whitlow 2007
(217) Evans 2006	(235) Kallmes 2008	(253) Mehdizade 2004	(15) Zhang 2008
(218) Figueiredo 2003	(236) Kallmes 2009a	(254) Murphy 2001	(271) Zhou 2008
(219) Fitousi 2006	(237) Kelekis 2005	(255) O'Brien 2006	
(220) Franco 2006	(238) Kim 2002	(256) Ortiz 2006	
(221) Gangi 1994	(239) Kobayashi 2006	(257) Perisinakis 2004	
(222) Gaughen 2002	(240) Komemushi 2005	(258) Pflugmacher 2005	

Reference numbers are presented in the parenthesis

Risk of bias in included studies

A graphical summary for the risk of bias of the 5 RCTs is included in our analysis in Figure 3.

Figure 3. Risk of bias summary.



Review authors' judgements about each methodological quality item for each included study
"+" = YES
"–" = NO
"?" = UNCLEAR

Although the allocation concealment was good in all 5 RCTs, there were 3 studies (Klazen 2010, Rousing 2009, and Voormolen 2007)with no blinding (25-27). There was also significant limitation in Voormolen 2007 study due to the small sample size and short follow-up period.

Allocation

In Buchbinder 2009, to ensure concealment of the assigned intervention, the treating radiologist obtained the opaque, sealed envelope containing the patient'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 .

In the study protocol conducted by Kallmes 2009, the group assignments were concealed from all patients and study personnel who performed follow-up assessments for the duration of the study. Only the study statisticians, who did not have any contact with the patients, saw unblended data. Then patients were randomly assigned to undergo either the full vertebroplasty procedure or the control intervention after the patient was prepared for surgery.

In Klazen 2010, upon obtaining informed consent an independent central telephone operator completed the randomisation procedure, using a computer programme. The maximum allowed unbalance (block size) was six, with a maximum sample size of 84 for each participating centre.

In Rousing 2009, the envelopes were prepared beforehand by the investigating surgeon and sorted randomly. The type of treatment was unknown to the patient and the investigators until after the patient had given written consent but the authors stated that because of the nature of the intervention blinding was not possible.

In Voormolen 2007, the patients were randomized in 2 groups by an independent central operator but no further information is provided regarding the allocation concealment.

Blinding

Blinding of patients was achieved by conducting a sham procedure in Buchbinder 2009 and Kallmes 2009 studies. In Buchbinder 2009 with the exception of the radiologist doing the procedure, other personnel were blinded to treatment assignments. Baseline data, were collected by a blinded assessor and at follow-up time points all participants were evaluated with the use of mailed questionnaires at 1 week and 1, 3, and 6 months after randomization.

In Kallmes 2009, the assignment was revealed to the clinician in the procedure room after the subject was sedated and had received local anesthesia. According to the study protocol, study-group assignments were concealed from all patients and study personnel who performed follow-up assessments for the duration of the study. Only the study statisticians, who did not have any contact with the patients, saw unblinded data.

Patients in the Klazen 2010, Rousing 2009 and Voormolen 2007 studies were aware of the treatment they were receiving. In Klazen 2010 participants, physicians, and outcome assessors were aware of the treatment assignment. In Rousing 2009, physical tests were performed at the 3-month follow-up visit and it is likely that the assessors were not blinded.

Incomplete outcome data

For assessment of the risk of bias due to incomplete data, we assumed more than 20% loss of data as high risk of bias. We also assessed each report for use of intention-to-treat analysis approach.

In Buchbinder 2009 study, the loss to follow-up was about 10% in both the intervention and the control group. There were 2 patients who crossed over from control to intervention and 1 who

crossed over from intervention to control before 1 month. Analysis was on the intention-to-treat basis.

In Kallmes 2009 study, the lost to follow-up before 1 month was 1% in the intervention group and 3% in the control group. Similar to the Buchbinder 2009 study, there were 2 patients who crossed over from control to intervention and 1 who crossed over from intervention to control before 1 month. Analysis was on the intention-to-treat basis.

In Klazen 2010, 163 (81%) participants completed 1 year of follow-up. Missing data for pain, EQ-5D, QUALEFFO, and RMD scores were imputed with linear interpolation and last observation carried forward. Imputation of missing data increased the power, but did not affect the results.

In Rousing 2009 study, the loss to follow-up was about 8% in the intervention and 4% in the control group. According to Rousing 2009, the intention-to-treat analysis was not relevant because the main outcome was pain at 3 months so analysis was performed just for those with available data.

In Voormolen 2007 study, all patients completed pain questionnaires before and both 1 day and 2 weeks after randomization. Analysis was on the intention-to-treat basis.

Selective reporting

All 5 RCTs reported pain as their main outcome measure. However they reported it at different time points. We organized reported data at 7 time points: baseline (the time of vertebroplasty or decision to not perform vertebroplasty), 1 to 3 days, 1 to 2 weeks, 1 month, 3 months, 6 months and 12 months.

Other potential sources of bias

Bias due to funding sources

The study by Buchbinder 2009 was partly supported with industry funding. The funding source of the Voormolen 2007 study was not clear. Although Buchbinder 2009 was partly supported by the industry but the trial did not conclude any additional benefit for PV.

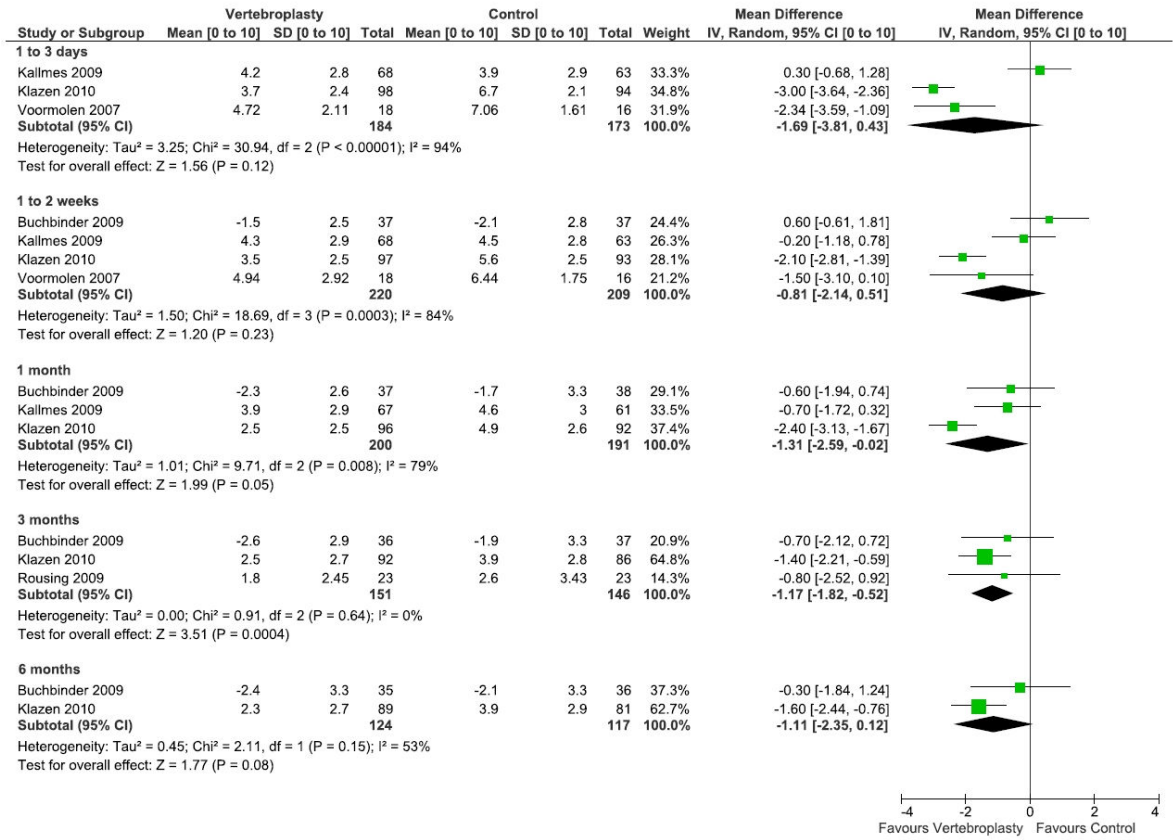
Efficacy analysis

We included 5 RCTs with 495 patients where 251 randomized to PV and 244 to control.

Pain

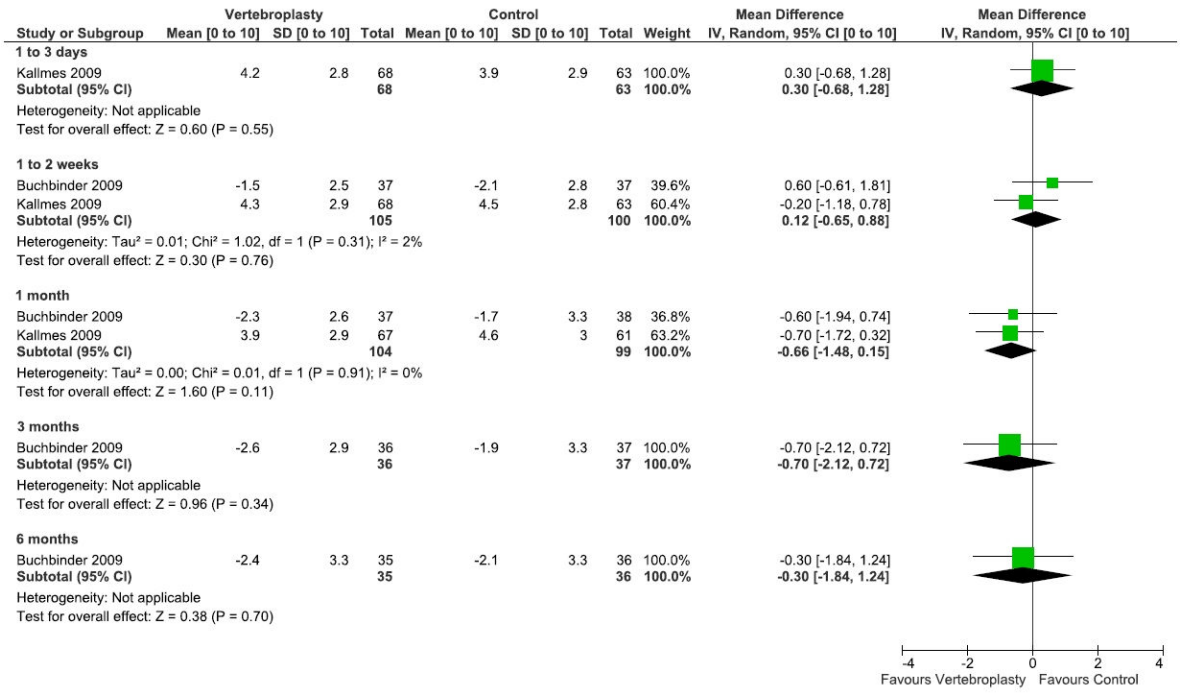
The primary outcome of this review is pain due to osteoporotic VCF. Our meta-analysis showed that there was no significant difference in pain between the intervention and control group at 1 to 3 days, 1 to 2 weeks, 1 month and 6 months follow-up. However we noted that the exclusion of unblinded RCTs will reinforce these findings and inclusion of unblinded RCTs will shift the mean difference favouring the vertebroplasty. When all RCTs were included the mean difference in pain at 3 months was statistically significant in favour of vertebroplasty. Forest plots are provided for the analysis when all RCTs are included (Figure 4) and when only the blinded RCTs are included (Figure 5).

Figure 4. Forest plot for pain at different follow-up time points when all RCTs (blinded and unblinded) were included.



When all RCTs included (blinded and unblinded) in the meta-analysis, there was a significant degree of heterogeneity with I^2 values of 53, 79, 84 and 94%.

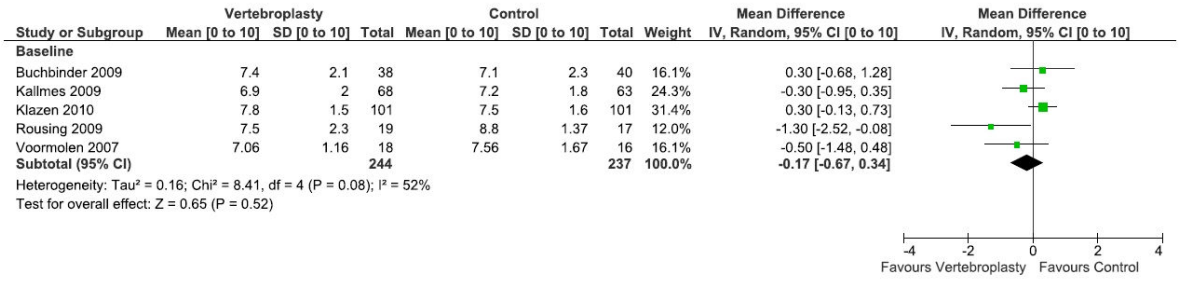
Figure 5. Forest plot for pain at different follow-up time points when unblinded RCTs were excluded.



When unblinded RCTs excluded from the meta-analysis, the homogeneity of data considerably improved. But data from both blinded RCTs were only available at 2 time points (1-2 weeks and 1 month).

Pain was measured either on a VAS or NRS in all 5 RCTs at baseline and different time points of follow-up. We tested pain outcome data for heterogeneity at baseline. A forest plot of Pain at baseline showed acceptable homogeneity of data across studies (Figure 6).

Figure 6. Forest plot for pain at baseline.



Forest plot for Pain at baseline showed acceptable homogeneity of data across studies.

Pain at 1 to 3 days follow-up was measured in Klazen 2010, Kallmes 2009 and Voormolen 2007, and the meta-analysis showed no statistically significant difference. Buchbinder 2009, Klazen 2010, Kallmes 2009, and Voormolen 2007 measured pain at 1 to 2 weeks follow-up, and did not show a significant statistical difference between the intervention and the control group as well. Pain at 1-month follow-up, was measured by Buchbinder 2009, Klazen 2010 and Kallmes 2009 did not show significant statistical difference between the intervention and the control group. Buchbinder 2009, Klazen 2010, and Rousing 2009 measured pain at 3-months follow-up and the meta-analysis showed significant statistical difference between the intervention and the control group. Pain at 6 months follow-up was measured by Buchbinder 2009 and Klazen 2010 and did not show significant statistical difference between the intervention and the control group. The trial published by Voormolen 2007 did not report the variance on pain. We received additional information from the principle investigator of the Voormolen 2007 regarding the variance in 2008.

Diasability

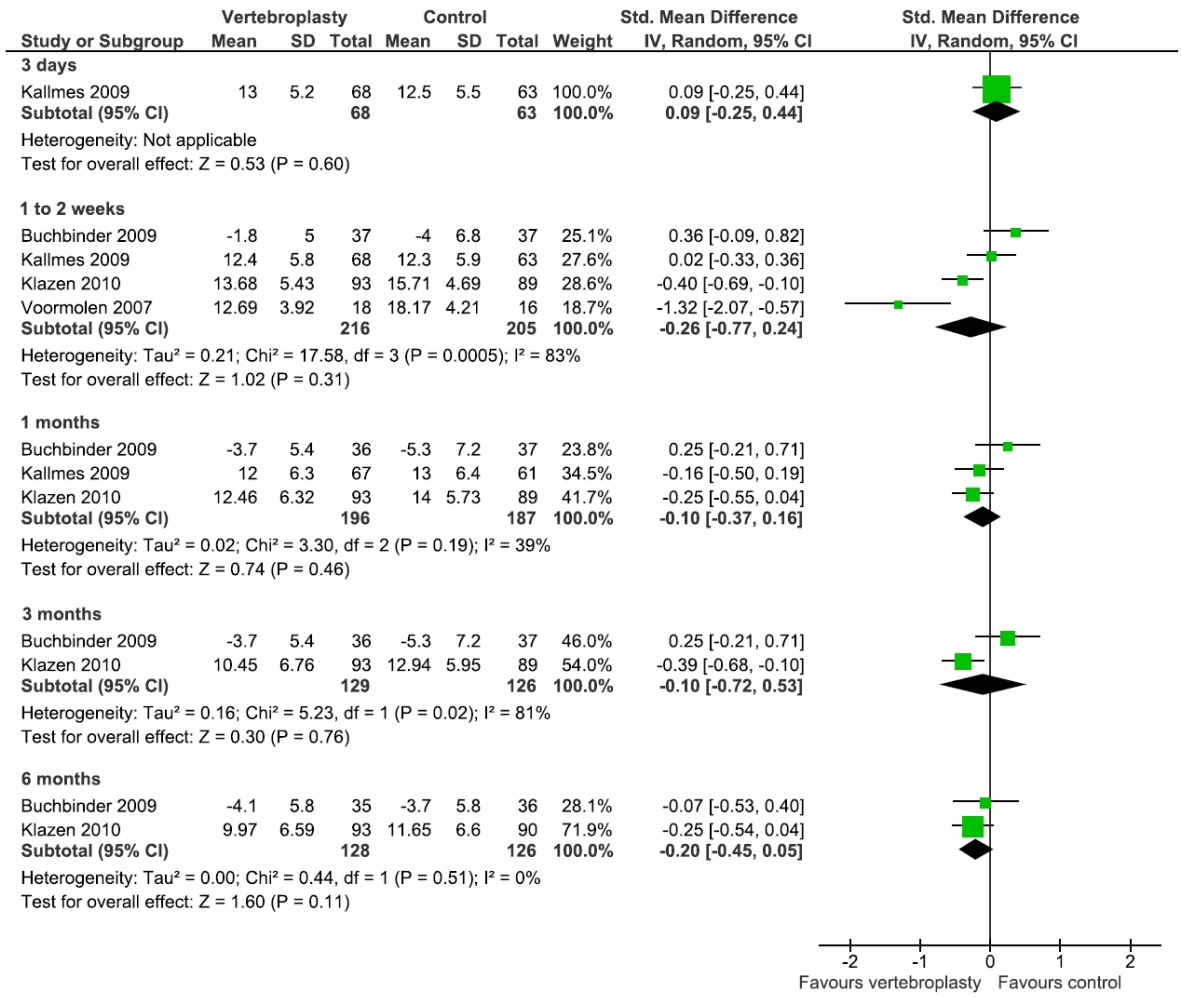
Diasability was measured either on the original (Klazen 2010 and Voormolen 2007) or modified (Buchbinder 2009 and Kallmes 2009) version of the Roland-Morris Disability Questionnaire.

Both questionnaires measure disability from low back pain with a higher score indicating worse disability. With a maximum score of 24 (original) or 23 (modified) a 2-3 point difference is felt to represent the minimal clinically important difference (272). There was no significant difference in disability between the intervention and the control group at 3 days, 1-2 weeks, 1 month, 3 months, and 6 months follow-up.

The Roland-Morris Disability Questionnaire was added to the protocol of Buchbinder 2009 in June 2005 to allow comparison with outcomes in the INVEST trial by Kallmes 2009. We used the Standardized Mean Difference approach to address the small difference in the tools used for measuring the "disability" outcome.

Disability at 3 days follow-up was only measured in Kallmes 2009 and showed no statistically significant difference. At 1-2 weeks follow-up time, Klazen 2010 and Voormolen 2007 reported significant improvement in the vertebroplasty group but the standardized mean difference did not show a significant statistical difference with an overall effect of Z equal to 1.02 (P = 0.31). Disability at 1-month follow-up measured by Buchbinder 2009, Kallmes 2009 and Klazen 2010 again did not show significant statistical difference between the intervention and the control group. Disability at 3 and 6-months follow-up was only measured by Buchbinder 2009 and Klazen 2010 did not show significant statistical difference between the intervention and the control group. In summary, there was no significant difference in disability between the intervention and the control group at 3 days, 1-2 weeks, 1 month, 3 months, and 6 months follow-up (Figure 7).

Figure 7. Forest plot for "Disability" at different time points.



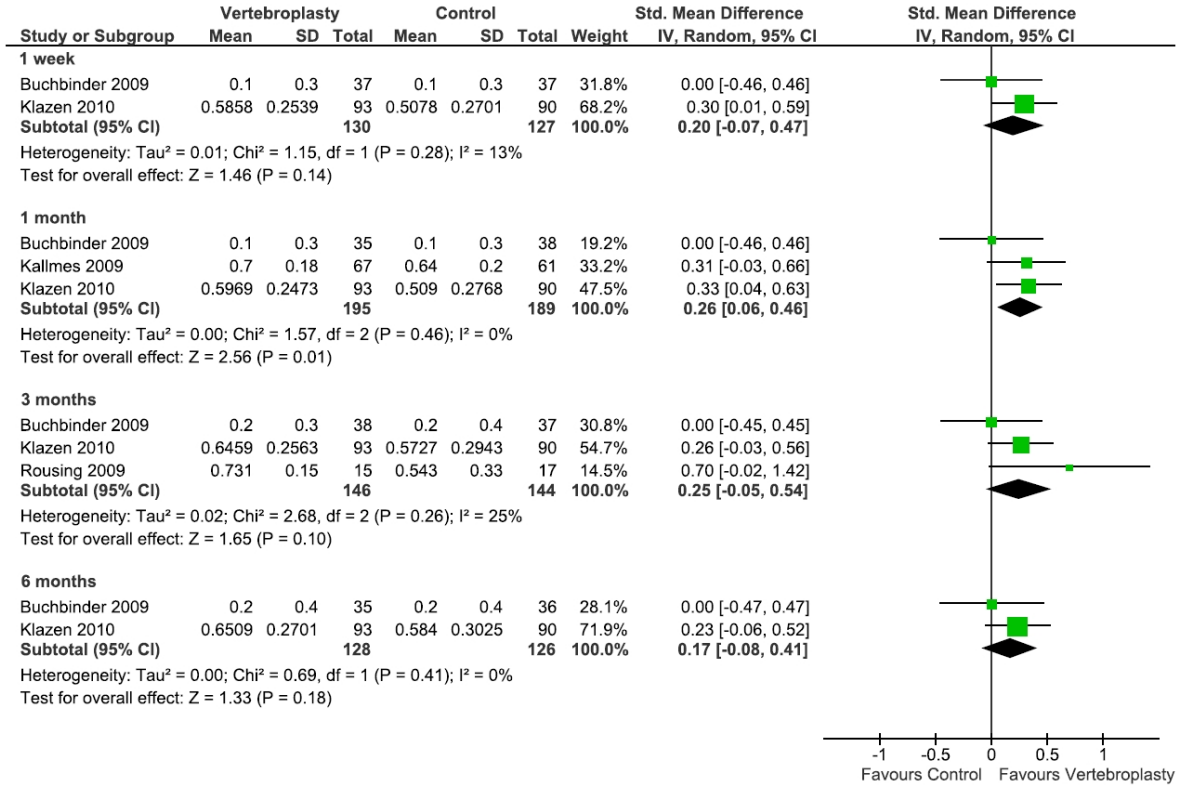
Forest plot for disability at different follow-up time points showed no statistically significant difference between the intervention and the control group.

Klazen 2010 and Voormolen 2007 did not report the details of data on disability. We received additional information from the principle investigators of the Klazen 2010 and Voormolen 2007 studies. Hetrerogeneity of data among the 4 included trials for disability was considerably high with I^2 of 83% at 1-2 weeks and 81% at 3 months.

Health-related Quality of Life (HR QOL)

There was significant difference in HR QOL between the intervention and the control group at 1 month with a standardized mean difference of 0.26 (0.06-0.46) with a P value of 0.01 (Figure 8).

Figure 8. Forest plot for "HR QOL" at different time points.



Forest plot for HR QOL on EQ5D at different follow-up time points showed statistically significant difference (P = 0.01), between the intervention and the control group at 1 month in favour of vertebroplasty with a standardized Mean Difference of 0.26 (0.06 – 0.46).

The 3 different tools used for measuring HR QOL in the RCTs were: 1) Scores on the Assessment of Quality of Life (AQoL) in Buchbinder 2009, 2) Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) in Buchbinder 2009, Klazen 2010 and Voormolen 2007, and 3) European Quality of Life with 5 Dimensions (EQ-5D) in Buchbinder 2009, Kallmes 2009, Klazen 2010 and Rousing 2009. We chose to conduct analysis on EQ-5D as it was reported in 3 RCTs.

HR QOL at 1-week follow-up measured by Buchbinder 2009 and Klazen 2010 on EQ-5D did not show a significant statistical difference between the intervention and the control group. HR QOL at 3 months follow-up measured by Buchbinder 2009, Klazen 2010 and Rousing 2009 did not show significant statistical difference between the intervention and the control group. Buchbinder 2009 and Klazen 2010 measured HR QOL at 6 months follow-up and did not show significant statistical difference between the intervention and the control group.

Safety analysis

We considered all 250 studies for report of adverse events. Most of reports of adverse events were presented as a case report or case series without a comparator or control group. However those adverse events could never have happened if the patient had not undergone vertebroplasty. In total adverse events were summarized from the pooled data of more than 16,000 patients with OVCF who received PV at about 23,000 levels.

1. Death directly related to PV

Although rarely reported, there were 10 cases of mortality directly related to PV. General post-operative causes such as complications of anaesthesia and infection were the etiologic factor in 5 cases. Other causes included pulmonary thromboembolism, fat embolism, pulmonary cement embolism (PCE) and extensive local cement leakage. The complete list of reported mortality cases is presented in Table 4.

Table 4. Mortality reports following vertebroplasty*

Study	Mortality	Time	Cause	Reference
Amar 2001	2	1 in the 1st day, 1 in the 3rd month	stroke, respiratory failure after reversal of general anesthesia complicated preexisting pneumonia	(32)
Martin 1999	2	1 in the 3rd day, 1 in 1 week	pain and cachexia, aspiration pneumonia after general anesthesia	(123)
Monticelli 2005	1	During PV	fatal pulmonary cement embolism	(132)
Patel 2007	2	1 after the PV and 1 within 7 days	pulmonary embolism, acute renal and cardiopulmonary failure	(139)
Syed 2006a	1	5 hours post-PV	fatal fat embolism	(167)
Tseng 2009	1	NA	post-operational sepsis	(178)
Wagner 2006	1	30 days	anterior cement displacement 1 cm into the retroperitoneal space & patient refused further treatment	(190)

There were 10 reported deaths directly related to vertebroplasty procedure.

2. Cement embolism to great vessels, heart and lung

Pulmonary cement embolism (PCE) was reported in 56 cases that underwent vertebroplasty. Most cases of PCE had transient respiratory symptoms and diagnoses were confirmed on follow-up CT scans. Significant distant cement emboli required surgical removal in 5 patients who experienced PCE (less than 10%). In 2 cases surgery was performed to remove cement emboli from the inferior vena cava (40;156). Surgical removal of cement was needed in 2 cases with emboli in the right heart chambers (49;97). There was also 1 case that needed surgical cement removal from the right pulmonary artery (69). Only 2 patients from the reported PCE cases (less than 4%), died due to severe PCE (132;139). The complete list of all reported cases of PCE is provided in Table 5.

Table 5. Adverse Events - Pulmonary Cement Embolism (PCE)*

Study	Number of Reported Cases with PCE	Reference
Amar 2001	3	(32)
Anselmetti 2005	2	(206)
Anselmetti 2008	1	(34)
Barbero 2008	4	(38)
Baumann 2006	1	(40)
Caudana 2008	2	(48)
Caynak 2009	1	(49)
Diel 2009	1	(61)
Figueiredo 2009	1	(68)
Francois 2003	1	(69)
Freitag 2006	1	(71)
Gangi 2003	2	(73)
Grados 2000	1	(76)
Gray 2009	3	(77)
Jensen 1997	2	(87)
Kao 2008	1	(90)
Kim 2005a	1	(97)
Klazen 2010	1	(25)
Ko 2009	1	(100)
Koch 2007	1	(102)
Layton 2007	8	(107)
Legroux-Gerot 2004	1	(111)
Liliang 2007	1	(115)
Masala 2009a	2	(125)
Monticelli 2005	1	(132)
Muijs 2009	1	(133)
Patel 2007	1	(139)
Purkayastha 2005	1	(146)
Quesada 2006	1	(147)
Righini 2006	1	(149)
Seo 2005	1	(156)
Tanigawa 2006a	1	(168)
Tanigawa 2009	2	(170)
Teng 2006	1	(172)
Vcelak 2009	1	(183)
Zaccheo 2008	1	(201)

** There were 56 reported cases of PCE diagnosed during or after the vertebroplasty procedure*

3. Complications of PV that required surgical intervention

Surgical intervention was required for treatment of complications in 60 patients following PV. Decompression of local cement leakage was required in 41 patients or 68.3% of the complications that required surgery. In 14 cases surgery was needed to deal with post-operative local infection. In 5 cases, cement leakage resulted in distant emboli that required surgical removal. The complete list of complications that required surgery is presented in Table 6.

Table 6. Adverse Events - Complications of PV requiring surgical intervention

Study	Adverse event requiring surgery	Day*	Reference
Alvarez 2006	1 Massive epidural leak	25	(31)
Amar 2001	1 Increased pain due to intra-discal leak	NA	(32)
Baumann 2006	1 Endovascular cement emboli in IVC	5	(40)
Birkenmaier 2007	1 Epidural hematoma and paraplegia	NA	(42)
Bouvresse 2006	1 Pott's disease requiring laminectomy	30	(43)
Caynak 2009	1 Cardiac tamponade (600 ml. of blood and cement particles)	60	(49)
Chen 2006	1 Bilateral leg weakness, ileus and abdominal distension due to Intradural leak	2	(52)
Cheung 2006	2 Epidural leak	NA	(53)
Cosar 2009	1 Subdural leak, 1 Subdural hematoma with paraparesis, urinary and fecal incontinence, 1 severe pain extending to the right lower extremity due to cement leak into the right neural foramen	NA	(56)
Francois 2003	1 Large pulmonary cement embolus in Right main pulmonary artery removed through a femoral venous approach	2	(69)
Hochegger 2005	1 Spinal stenosis with reduced sensation and power on lower extremities and displaced fracture fragmented required surgery for corporectomy of L3 and stabilization	120	(85)
Kallmes 2009a	1 Osteomyelitis required debridement surgery	14	(236)
Kim 2005a	1 Embolism to heart with perforation of RV and embolism to Lungs required open heart surgery	6	(97)
Kumar 2005	1 Epidural cement leak causing paraparesis required decompression surgery	1	(7)
Lopes 2004	1 Excruciating pain in distribution of right intercostal nerve T6 and hyperemia required interruption of vertebroplasty procedure and bilateral T5-7 laminectomy after 7 hours	0	(120)
Mirovsky 2006	2 Epidural cement leak removed by surgery	NA	(131)
Mummaneni 2006	2 Inections required corpectomy and fusion	NA	(134)
Rapan 2009	1 Cement leak into the spinal canal	0	(148)
Sabuncuoglu 2008	1 Right lower limb weakness due to intradural cement leak	NA	(152)
Schmidt 2005	2 Significant cement leak required laminectomy and surgical decompression for removal of cement	NA	(154)
Seo 2005	1 IVC and Left atrium cement embolus	730	(156)
Shapiro 2003	1 Back pain, bilateral sciatica and bilateral lower extremity weakness	0	(158)
Sonmez 2010	1 Weakness of the right great toe dorsiflexion, and hypoesthesia on the L5 dermatome required microdiscetomy	14	(161)
Soyuncu 2006	1 Infection required surgery for abscess drainage	7	(162)
Teng 2006	1 Complete paraplegia and lower extremity sensory loss, 1 weakness on both lower extremities and inablity to walk with incontinence, 1 urine and stool incontinence and inability to move lower extremity against gravity	NA	(172)
Tsai 2003	1 Ant. Cortical breakdown with cement displacement causing kyphosis, cord compression and reduced leg reflexes	30	(176)
Tseng 2009	6 Patients required surgery (3 laminectomy, 1 laminectomy and internal fixation, 2 wound complications)	NA	(178)
Vats 2006	1 Persistent pain and impaired ambulation. Bilateral L4-5 laminectomy	NA	(182)
Wu 2007	1 Lower extremity weakness, paraesthesia and radicular pain required laminectomy	120	(195)
Yang 2008	17 Patients required surgery for infection, cement dislodgement, fragmentation or poor augmentation	NA	(197)
Yu 2004	1 Pyogenic spondylitis and paraspinal abscess at T12	30	(199)

** Time of surgery after vertebroplasty in days*
NA = Not Available

4. New osteoporotic vertebral fractures after vertebroplasty

In 53 studies, patients were monitored for occurence of new osteoporotic vertebral compression fractures in the follow-up period. The mean follow-up time was 396 days (SD = 347) and 1,666 new fractures were reported in 7385 patients who underwent vertebroplasty. There were no control group in these studies to allow a comparison in the rates of the new incidences of vertebral compression fractures.

5. Local cement leakage

Local cement leakage is well known to be the most common adverse event of PV. In most cases of local cement leakage patients express no complaint and the diagnoses are usually made by follow-up CT scans of the vertebrae. In symptomatic cases, symptoms are mainly due to pressure of hardened cement mass on either the spinal cord or spinal nerve roots. We included reports that collected data on 30 or more consecutive cases to capture frequency of various types of cement leakage. We categorized leakage types to: Paravertebral, Intradiscal, Epidural, Needle tract/Soft tissue, Foraminal, and Intradural. The most common type of local cement leakage is paravertebral with 21% frequency. The second most common type is intra-discal with 15% frequency. The third most common local cement leakage type is epidural with 12% frequency. The frequency of other types of cement leakages are: 5% for needle tract/soft tissue, 3% for Foraminal and less than 0.5% for intradural. Only a small proportion of cases become symptomatic which in most cases is less than 1 percent. However when present all intradural and 1 in 4 foraminal cement leakages are symptomatic. We provided the frequency table of local cement leakages in Table 7.

Table 7. The rate of various types of cement leakage in patients who received percutaneous vertebroplasty *

Cement leakage type	Number of included studies	Total PV* levels	Rate per 100 vertebral levels. Mean (SD)	Percent Symptomatic
Paravertebral	48	11,016	20.72 (21.70)	0.02
Intradiscal	43	9,804	14.97 (9.80)	0.06
Epidural	37	7,412	11.95 (17.72)	2.41
Needle tract / Soft tissue	6	1,297	4.64 (2.56)	1.38
Foraminal	7	1,078	2.71 (2.13)	31.83
Intradural ◊	1	261	0.38 (NA)	100

** Note that in some cases there are more than one type of cement leakage reported at one vertebral level.*

◊ There were reports of 4 cases with intradural leakage in 4 different studies (all symptomatic), but only one report satisfied our selection criteria (leakage reported in 30 consecutive case or more).

Sensitivity Analyses: Effect of study quality

Our criteria for judgement on study quality were adequate allocation concealment and blinding. Based on these criteria results from the Buchbinder 2009 and Kallmes 2009 studies with adequate allocation concealment and blinding were analyzed separately. When all 5 RCTs included, the analyses did not show significant change except for HR QOL at 1 month.

Chapter 4: Discussion

Efficacy

Pain due to the osteoporotic VCF was the primary outcome in our analysis. Pain was assessed at baseline and multiple follow-up time points. Our meta-analysis showed no significant statistical difference in pain between the PV and the control groups except at 3 months, which was in favour of vertebroplasty. Although pain on VAS at 3 months was statistically significant with a Mean Difference of -1.17 (-1.82 to -0.52) it was very close to our pre-determined minimum threshold of clinically important change of 1 point.

Voormolen 2007 showed significant difference in pain on VAS (-2.34 with a Confidence Interval of -3.59 to -1.09) at 1 day follow-up as well as a slight advantage of PV over the control group at 2 weeks (not statistically significant) with a mean difference of -1.50 in pain on VAS and a Confidence Interval of -3.10 to 0.10. In his report Voormolen 2007 assumed that the non-statistically significant result at 2 weeks could be attributed to occurrence of 2 new VCF in the PV group. Klazen 2010 showed significant difference in pain on VAS in favour of vertebroplasty at 1 day, 1 week, as well as 1, 3, 6 and 12 months.

Disability was assessed using the original or the modified version of the Roland-Morris Disability Questionnaire. Buchbinder 2009, Kallmes 2009, Klazen 2010 and Voormolen 2007 assessed disability in different time points but only Klazen 2010 and Voormolen 2007 reported significant improvement in the intervention (vertebroplasty) over the control group at 1-2 weeks. Buchbinder 2009 showed no significant difference between the PV and the control group at 1 week as well as 1,

3 and 6-month follow-up times. Results from Kallmes 2009 showed no significant improvement after PV when compared to control on 3 days and 2 weeks follow-up. The heterogeneity of data for disability was considerably high among the studies.

HR QOL meta-analysis was performed on results from EQ 5D utility assessment (0 to 1 for perfect health) with a minimum clinical difference of 0.074. HR QOL on EQ 5D was assessed by Buchbinder 2009, Kallmes 2009, Klazen 2010 and Rousing 2009 and showed significant difference between the PV and the control group at 1 month with a standardized mean difference of 0.26 (0.06-0.46). There was no significant difference between the vertebroplasty and control group at 1 week, 3 months and 6 months.

Safety

Severe adverse events following PV are not commonly reported. However, we identified 10 reports of death directly related to the PV procedure. There were reports of 60 cases with complications of PV that required surgical intervention as well as 56 cases of PCE. Local cement leakage is the most common complication of PV but most are asymptomatic and diagnosed on follow-up CT scans.

Overall completeness and applicability of evidence

We identified 5 RCTs that were conducted to determine the efficacy of PV. There was a considerable heterogeneity among the included studies. All trial participants were suffering from painful osteoporotic VCF. Duration of the disease varied across trials but the levels of pain at baseline were comparable (Figure 6). A detailed assessment of co-morbidities in the trial patients

was presented in Kallmes 2009 in the form of Charlson indices (273). Adverse events were also reported in the trials but due to the rarity of adverse events we investigated a larger pool of reports that included observational studies. Klazen 2010 collected cost data beside the clinical outcomes.

Quality of the evidence

There were only 2 RCTs with adequate allocation concealment and blinding (23;24). Prior to the RCTs many case series have been published as well as 3 controlled-before and after studies. Buchbinder 2009 and Kallmes 2009 did not achieve the targeted sample size however; they maintained the power of the studies within acceptable range. According to the Buchbinder 2008 protocol, for detection of a large advantage of PV over control (assuming at least 2.5 units greater improvement on VAS) they calculated a sample size of 24 for each group. However, for detecting a smaller advantage of 15% (assuming a mean PV improvement of 4.0 units compared to mean improvement of 2.5 units in the control group) they estimated that 64 patients are needed to be enrolled in each group. The INVEST study protocol (274) estimated that they need to enrol 166 patients to achieve 75 patients at each arm of study after 1 month (assuming 10% loss to follow-up). A sample size of 150 at 1 month would have yield greater than 95% power for detection of difference of 1.75 (on 0 to 10 VAS) and a greater than 80% power to detect a 1.25 unit difference. The final sample size of 131 Kallmes 2009 study achieved power of 89% to detect 1.5 unit difference in VAS for pain.

Potential biases in the review process

The recent assessments of the published evidence show there is still a tendency toward publishing trials with positive findings (275). Due to the limited number of available RCTs on efficacy of PV, the publication bias in this review cannot be ruled out. However, it should be mentioned that 3 of the total 5 RCTs for efficacy of PV, reported no additional benefits.

It is shown that in some cases exclusion of non-English papers from the meta-analyses resulted in completely different conclusions (276). We had no language limit in our search strategy thus avoiding a language bias. We did not identify any RCT on PV published in other languages.

Agreements and disagreements among studies

Alvarez 2006 (31), Diamond 2006 (60) and Nakano 2006 (137) were 3 reports with controlled before and after design on PV. They all reported significant efficacy of PV when compared to a control group. A summary of the results from these 3 studies is presented in Table 1.

Alvarez 2006 compared 101 consecutive patients who underwent PV with 27 patients who refused PV and were managed conservatively. Patients with PV had significantly more pain and functional impairment before the procedure than the patients of the conservative group. Alvarez 2006 concluded that PV provided significant pain relief and improved the quality of life when compared to the control group. The size of the control group was very small when compared to the intervention group. The distribution of 14 patients who were lost to follow-up is not clear among the PV and the control group. These patients were excluded from the analysis.

Diamond 2006 conducted a non-randomised study on 126 patients over a 2-year follow-up period. Patients with painful and acute osteoporotic VCF (within 1 to 6 weeks) that was not relieved by oral analgesia participated in the study. Comparison was made between 88 patients who underwent PV and 38 patients who declined PV and were managed conservatively. The study reported that PV patients had significantly better improvement in pain, a rapid return to normal function and lower rates of hospitalisation. The lower pain scores persisted in the PV group at 6 weeks, but no differences between the two groups were evident at 12 and 24 months.

Nakano 2006 compared 30 consecutive patients with osteoporotic VCF who underwent PV with a matched control group consisting of historical hospital data from 30 patients were treated conservatively (prior to the availability of PV in the hospital). Patient in the control group were matched for age, sex, interval from injury to treatment, and grade of the posterior wall defects of the fractured vertebral body. Outcome measures included back pain on VAS, analgesic requirements, and the radiographically documented rate of the vertebral body kyphosis. The mean follow-up duration was 17 months. Nakano 2006 concluded that back pain significantly improved in the PV group and the mean duration of analgesic requirement in PV group (8.3 days) was significantly less than 62.2 days in the control group. The report stated that the control sample consisted of 59 participants who met the inclusion criteria and who agreed to longitudinal evaluation but it is not clear why data from 29 were excluded in the analysis. Patients in both groups received conservative management and there was no mention of withdrawals or drop outs.

There were 2 reviews that concluded PV is beneficial (277;278). These reviews considered some of the above-mentioned 3 studies (Alvarez 2006, Diamond 2006 and Nakano 2006) as well as results from other observational reports of case series. They suggested that RCTs are needed and recognized the lack of randomization as one of the main concerns. Similar to Alvarez 2006, Diamond 2006 and Nakano 2006 there was also concern regarding allocation concealment and blinding in Klazen 2010 and Voormolen 2007.

There was a significant heterogeneity among the 5 identified RCTs (Figures 4 and 7). One could say that the lack of randomization and blinding should satisfactorily explain the differences between the findings of 2 blinded RCTs (Buchbinder 2009 and Kallmes 2009) with other studies. We also explored other possible explanations for the differences. However the striking aspect of the Buchbinder 2009 and Kallmes 2009 studies was that PV and conservative management were equally effective in significant reduction of pain and improving disability and health-related quality of life rather than being equally ineffective. This important observation would primarily suggest the placebo effect. It is shown that the placebo effect has strong association with the patient's treatment preference. The effect of preference on trial outcome depends on the proportion of participants with a certain preference, the effect of the preference on the perceived subjective outcome i.e. pain, and the true effect size of the intervention (279). In Kallmes 2009, of those who crossed over at 3 months, 20 of 27 patients (74%) in the control group and 2 of 8 patients (25%) in the intervention group correctly guessed their treatment assignment. Kallmes 2009 suggested the possibility of more effectiveness of PV than the control for a subgroup of patients.

It is possible that the patients were different in terms of the treatments they received for their pain prior to enrolment despite similarities in demographic characteristics and pain levels at baseline. We noted that patients in the control groups of Buchbinder 2009 and Kallmes 2009 had slightly higher rates of opioid analgesic use (63 versus 56% in Kallmes 2009 and 85 versus 79% in Buchbinder 2009). It is also well known that the duration and severity of back pain following osteoporotic VCF as well as patients' response to treatment varies from patient to patient (280). Baseline imbalance in trials with less than 400 participants could reduce the power (281).

In reports where the majority of the enrolled patients have back pain of a self-limiting nature, the 2 groups will express similar pain outcomes regardless of the efficacy of the intervention. One would think that randomization would compensate and prevent such problems, which is true, but essentially with significant increase in the sample size. The duration of symptoms in Klazen 2010 in

all study participants was 6 weeks or less. According to Buchbinder 2010, duration of symptoms in 32% of patients who were enrolled in Buchbinder 2009, and 41% of patients who were enrolled in Kallmes 2009 was less than 6 weeks but all patients had evidence of bone edema on MRI.

It seems logical to enrol only patients who have not responded to medical management. Kallmes 2009 and Voormolen 2007 included patients who had no adequate pain relief with medical management but it is not clear if they had similar criteria in defining medical management and inadequate response. It is also understood that patient enrolment was a major challenge in completion of RCTs and investigators decided to relax their selection criteria to enrol as many patients as possible. Kallmes 2009 allowed addition of the foreign sites to the study to have the number of subjects needed for an acceptable sample.

In summary, various types of bias including selection, measurement and analysis biases and differences in the quality of included studies could explain some degree of disagreement among the studies. However the existence of other causes of difference as confounders (i.e. differences in the progression of the osteoporotic VCF beyond demographic characteristics and pain at baseline), and chance (random variations in findings across the studies) could not be ruled out.

Conclusion

Implications for practice

Information from the currently available trials does not support efficacy of vertebroplasty for reducing pain and improving disability and health-related quality of life. The only exception was Health Related Quality of Life at 1 month that showed additional improvement in the vertebroplasty group with a standardized mean difference of 0.26 (0.06-0.46). Severe adverse effects following vertebroplasty are rare. More than 80% of the reports on PV adverse events have been published in the last 5 years (2004 to 2010). This could be due to the widespread use of PV over the last few years. Notably, the reports of the adverse events suggest that the frequency and severity of the events are operator and technique dependent. The majority of vertebroplasties performed by the interventional radiologists but it was noted that half of the reported mortality following vertebroplasty are among those patients who underwent vertebroplasty by other specialist physicians. Introducing internationally recognized training and certification guidelines for the performance of PV could play a significant role in the prevention of catastrophic adverse events. Severe adverse events can occur following PV and so far the evidence regarding the clinical benefit of PV is quite limited. Therefore, until more evidence is available, the decision to perform PV should be based on very strict criteria. Probably, the most critical issue surrounding the decision to perform PV is the definition of "failed conservative management". This might be "no adequate response to pain management with conservative treatments" with clear guidelines for the prescription of narcotic analgesia, high dose Calcitonin and non-pharmacological measures for a specified minimum period of time.

Implications for research

More high quality RCTs for assessment of PV efficacy are needed. Baseline imbalance and patient treatment preferences should be taken into account in the analysis of findings in vertebroplasty RCTs. The majority of patients with osteoporotic VCF are asymptomatic and those with back pain usually respond to conservative management. Kallmes 2009 and Voormolen 2007 attempted to address this issue by including patients with no adequate pain relief with standard medical therapy. However, it is not clear what is being referred to as "inadequate pain relief" and "standard medical therapy". Therefore, the optimum setting of a trial would be to treat all patients with painful osteoporotic VCF for an introductory period of 4 to 6-week according to a standard conservative management protocol. Those patients who did not adequately respond to the medical management would be then eligible to participate in the second stage of the study where they are randomization to PV or the sham procedure. After randomization to either PV or the sham procedure, patients will continue to receive conservative treatment as required. This would provide the opportunity to answer a crucial question: "Do patients with inadequate response to conservative management benefit from PV?"

The most challenging barrier in conducting a randomized study on PV has proven to be the "patient recruitment". Similar to other interventions with global implementation prior to establishment of the efficacy, patients would be reluctant to participate in a study where they are aware of the possibility of being randomized to a sham procedure. Patient enrolment will be encouraged in a study where the initial standard conservative management period is proven effective in the majority of patients and the medical management is guaranteed to continue for those patients with no adequate response to pain management regardless of their study group assignment.

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Appendices

Appendix 1: Literature search strategy

a. Original search strategy in MEDLINE

The following search strategy was the original strategy developed for MEDLINE for this review:

1. exp Spine/
2. (spine or spinal or vertebra$).tw.
3. exp Fractures, Bone/
4. fractur$.ti.
5. 1 or 2
6. 3 or 4
7. 5 and 6
8. exp Spinal Fractures/
9. 7 or 8
10. exp Bone Cements/
11. exp Methylmethacrylates/
12. methacrylate$.tw.
13. bone cement$.tw.
14. exp Fracture Fixation, Internal/
15. or/10-14
16. 9 and 15
17. vertebroplast$.tw.
18. cementoplast$.tw.
19. sacroplast$.tw.
20. or/16-19
21. randomized controlled trial.pt.
22. controlled clinical trial.pt.
23. randomized controlled trials.sh.
24. random allocation.sh.
25. double blind method.sh.
26. single-blind method.sh.
27. or/21-26
28. (animal$ not human).sh.
29. 27 not 28
30. clinical trial.pt.
31. exp clinical trials/
32. (clin$ adj25 trial$).ti,ab.
33. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw.
34. placebo$.sh.
35. placebo$.ti,ab.
36. random$.ti,ab.
37. research design.sh.
38. or/31-37

39. 38 not 28
40. 39 not 29
41. comparative study.sh.
42. exp evaluation studies/
43. follow up studies.sh.
44. prospective studies.sh.
45. (control$ or prospectiv$ or volunteer$).ti,ab.
46. or/41-45
47. 46 not 28
48. 47 not (29 or 40)
49. 20 and 48
50. limit 49 to yr="1987 - 2007"

b. MEDLINE search strategy

The search was conducted on Ovid MEDLINE(R) 2007 to September 2010

1. exp Spine/
2. (spine or spinal or vertebra$).tw.
3. exp Fractures, Bone/
4. fractur$.ti.
5. 1 or 2
6. 3 or 4
7. 5 and 6
8. exp Spinal Fractures/
9. 7 or 8
10. exp Bone Cements/
11. exp Methylmethacrylates/
12. methacrylate$.tw.
13. bone cement$.tw.
14. exp Fracture Fixation, Internal/
15. or/10-14
16. 9 and 15
17. vertebroplast$.tw.
18. cementoplast$.tw.
19. sacroplast$.tw.
20. or/16-19
21. randomized controlled trial.pt.
22. controlled clinical trial.pt.
23. randomized.ab.
24. placebo.ab.
25. drug therapy.fs.
26. randomly.ab.
27. trial.ab.
28. groups.ab.
29. or/21-28
30. (animals not (humans and animals)).sh.
31. 29 not 30
32. 20 and 31

c. CINAHL search strategy

This search strategy was repeated in August 2010 to identify additional studies.

1. exp SPINE/
2. (spine or spinal or vertebra$).tw.
3. exp FRACTURES/
4. fractur$.tw.
5. 1 or 2
6. 3 or 4
7. 5 and 6
8. exp Spinal Fractures/
9. 7 or 8
10. exp Bone Cements/
11. exp METHYLMETHACRYLATES/
12. methacrylate$.tw.
13. bone cement$.tw.
14. exp Fracture Fixation/
15. or/10-14
16. 9 and 15
17. vertebroplast$.tw.
18. cementoplast$.tw.
19. sacroplast$.tw.
20. or/16-19
21. limit 20 to yr="1987 - 2007"

Update 2008 – 2009
S22 S17 or S18 or S19 or S20
S21 S17 or S18 or S19 or S20
S20 ti sacroplast* or ab sacroplast*
S19 ti cementoplast* or ab cementoplast*
S18 ti vertebroplast* or ab vertebroplast*
S17 S10 and S16
S16 S11 or S12 or S13 or S14 or S15
S15 (MH "Fracture Fixation")
S14 ti bone cement* or ab bone cement*
S13 ti methacrylate* or ab methacrylate*
S12 (MH "Methylmethacrylates")
S11 (MH "Bone Cements")
S10 S8 or S9
S9 (MH "Spinal Fractures+")
S8 S6 and S7
S7 S4 or S5
S6 S1 or S2 or S3
S5 ti fractur* or ab fractur*
S4 (MH "Fractures+")
S3 ab spine or spinal or vertebra*
S2 ti spine or spinal or vertebra*
S1 (MH "Spine+")

d. EMBASE search strategy

This search strategy was repeated in August 2010 to identify additional studies.

1. exp SPINE/
2. (spine or spinal or vertebra$).tw.
3. exp Fracture/
4. fractur$.tw.
5. 1 or 2
6. 3 or 4
7. 5 and 6
8. exp Spine Fracture/
9. 7 or 8
10. exp Bone Cement/
11. exp Methacrylic Acid Methyl Ester/
12. methacrylate$.tw.
13. bone cement$.tw.
14. exp Fracture Fixation/
15. or/1-14
16. 9 and 15
17. vertebroplast$.tw.
18. cementoplast$.tw.
19. sacroplast$.tw.
20. or/16-19
21. random$.ti,ab.
22. factorial$.ti,ab.
23. (crossover$ or cross over$ or cross-over$).ti,ab.
24. placebo$.ti,ab.
25. (doubl$ adj blind$).ti,ab.
26. (singl$ adj blind$).ti,ab.
27. assign$.ti,ab.
28. allocat$.ti,ab.
29. volunteer$.ti,ab.
30. crossover procedure.sh.
31. double blind procedure.sh.
32. randomized controlled trial.sh.
33. single blind procedure.sh.
34. or/21-33
35. exp animal/ or nonhuman/ or exp animal experiment/
36. exp human/
37. 35 and 36
38. 35 not 37
39. 34 not 38
40. 20 and 39
41. limit 40 to yr="1987 - 2007"

e. The Cochrane Library search strategy

This search strategy was repeated in August 2010 to identify additional studies.

DARE: 1
CENTRAL: 1
HTA: 1
NHS EED: 1

#1MeSH descriptor Spine explode all trees
#2 (spine or spinal or vertebra*):ti,ab
#3MeSH descriptor Fractures, Bone explode all trees
#4fractur*:ti,ab
#5(#1 OR #2)
#6(#3 OR #4)
#7(#5 AND #6)
#8MeSH descriptor Spinal Fractures explode all trees
#9(#7 OR #8)
#10MeSH descriptor Bone Cements explode all trees
#11MeSH descriptor Methylmethacrylates explode all trees
#12methacrylate*:ti,ab
#13bone cement*:ti,ab
#14MeSH descriptor Fracture Fixation, Internal explode all trees
#15(#10 OR #11 OR #12 OR #13 OR #14)
#16(#9 AND #15)
#17 vertebroplast*:ti,ab
#18cementoplast*:ti,ab
#19sacroplast*:ti,ab
#20(#16 OR #17 OR #18 OR #19)
#21(#20), from 1987 to 2006

f. Web of Science search strategy

This search strategy was repeated in August 2010 to identify additional studies.

#1TS=(vertebroplast* or cementoplast* or sacroplast*)
DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI, A&HCI; Timespan=1987-2009
#2TS=(spine or spinal)
DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI, A&HCI; Timespan=1987-2009
#3TS=(fractur*)
DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI, A&HCI; Timespan=1987-2009
#4#3 AND #2 AND #1

g. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

Search term = Vertebroplasty

Appendix 2: Sample record in the abstract selection form

Paper ID: 2374	R	S	X

Title: Percutaneous vertebroplasty for vertebral compression fracture

Abstract: BACKGROUND: Percutaneous vertebroplasty has become an option for the treatment of painful osteoporotic compression fractures in patients in whom conservative medical management has failed. AIM: This paper assessed the effectiveness and safety of percutaneous vertebroplasty in patients with focal pain caused by compression vertebral body fractures. MATERIALS AND METHODS: Over a twenty-five-month period 63 patients underwent percutaneous vertebroplasty, and ten of these patients were subsequently retreated, for a total of 73 operations on 93 vertebrae. The patients were affected by osteoporotic compression fractures (n=57) or by benign or malignant infiltrative processes (n=6). All patients were examined at discharge and thereafter to assess the level of pain and investigate possible changes in the quality of life. The mean length of follow-up was 15.2 months. RESULTS: After treatment, almost 90% of patients reported complete disappearance or significant alleviation of the pain. In 7 of 63 of the patient (11%) there were small asymptomatic leakages of cement outside the vertebral body. A substantial number of patients with osteoporosis, 19% of the study population, experienced new fractures following treatment with vertebroplasty. DISCUSSION: Our experience confirms the effectiveness of vertebroplasty to pain caused by vertebral fractures. If the indications are strictly followed, improvement of symptoms is often immediate, allowing the return of mobility, and patient satisfaction with surgery is higher. The use of appropriate systems limits the number of complications.

R = Include full-paper for "Efficacy" and "Safety" Review
S = Include full-paper only for "Safety" Review
X = Exclude

Appendix 3: Sample record in the full-paper selection form for "Efficacy"

Efficacy Paper Selection Form

Paper ID: 2374

Paper Title: Percutaneous vertebroplasty for vertebral compression fracture

1. Type of Study

☐ Controlled Study *(Controlled Clinical Trial, Controlled Before and After, etc.)*

☐ Interrupted Time Series *(a single-group design with multiple before and after measures)*

☐ Case Series *(a single-group design with at least one before measure)*

☐ Other: .....

2. Types of Participants

☐ Osteoporotic Vertebral Compression Fracture (OVCF)

☐ Mixed (Osteoporotic, Neoplasm, Hemangioma, etc.)

☐ Not OVCF

# of subjects with OVCF: [ ]

3. Types of interventions

☐ Vertebroplasty

☐ Mixed (vertebroplasty and kyphoplasty)

☐ Kyphoplasty (Balloon vertebroplasty)

# of subjects with vertebroplasty: [ ]

4. Types of outcome measures

- ☐ Pain
- ☐ Function or disability
- ☐ Health Related Quality of Life
- ☐ Change in height following the procedure
- ☐ Other, if possible please specify: .....

5. Tools used for measuring outcomes

- ☐ Visual Analogue Scale
- ☐ Numerical Rating Scale
- ☐ Roland-Moris Disability Questionnaire
- ☐ Oswestry Disability Index
- ☐ Short Form 36 items (SF36)
- ☐ Osteoporosis Quality of Life (OQL and miniOQL)
- ☐ Elderly Quality of Life
- ☐ Other, if possible please specify: .....

6. Average follow-up period (in days): [ ]

7. Crossover (in controlled studies)

- ☐ YES
- ☐ NO

Additional Comments:

Appendix 4: Sample record in the full-paper selection form for "Safety"

Safety Paper Selection Form

Paper ID: 2374

Paper Title: Percutaneous vertebroplasty for vertebral compression fracture

1. Type of Study

☐ Controlled Study *(Controlled Clinical Trial, Controlled Before and After, etc.)*	☐ Interrupted Time Series *(a single-group design with multiple before and after measures)*	☐ Case Series *(a single-group design with at least one before measure)*	☐ Other: .....

2. Types of Participants

A ☐ Osteoporotic Vertebral Compression Fracture (OVCF)	B ☐ Mixed (Osteoporotic, Neoplasm, Hemangioma, etc.)	C ☐ Not OVCF

# of subjects with OVCF: [ ]

3. Types of interventions

A ☐ Vertebroplasty	B ☐ Mixed (vertebroplasty and kyphoplasty)	C ☐ Kyphoplasty (Balloon vertebroplasty)

# of subjects with vertebroplasty: [ ]

4. If more than one case was reported, do the participants appear to have been consecutive?

YES ☐ NO ☐

5. Adverse effects during or after the procedure:

Event	Count	Time*
Death		
Pulmonary cement embolism		
New VCF		
Infection		
Any complication requiring surgery		
Increase in back pain		
Pulmonary distress		
Neurological complication (with details)		
Other new fracture		
Other:		

Cement leakage - Type	Symptomatic	Count
	Y / N	
	Y / N	
	Y / N	
	Y / N	
	Y / N	
	Y / N	
	Y / N	
	Y / N	
	Y / N	
	Y / N	

** Time is in reference to vertebroplasty. If more than one time point is identified for an event and the provided space is insufficient to record the information, please circle the event and provide information on the back of this form.*

6. Total number of spinal levels received vertebroplasty:

Additional Comments:

Appendix 5: Detailed data extraction form for RCTs

Page 1

Data Extraction Form

Reviewer:

Identification:
Article ID:

Title:

Trial authors:

Source of sponsorship:

Comments:

Trial Characteristics:
Total number of study groups:

Number of comparison groups:

Is this a multi-center trial?
( ) yes - how many centers are included?
( ) no

Country of origin of trial:

Setting:

Study Design:

Experimental Design: ☐ Parallel Group ☐ Crossover ☐ Open-label

Comments:

Intervention:

☐ Treatment ☐ Other (Specify)

Treatment Comparators:

☐ Placebo ☐ Other treatment ☐ Other:

Comments:

Dose:
Method of administration:
Frequency of administration:
Duration of treatment:
Any additional treatment during trial:

Appendix 5: Detailed data extraction form for RCTs

Page 2

Trial Methodology (additional comments):

Blinding: ☐ Double ☐ Assessor
☐ Single ☐ Patient
☐ Open ☐ Investigator

Data Analysis: ☐ Intention-to-treat

Participants:
Inclusion Criteria:

Exclusion Criteria:

Medication allowed:

Medication withdrawn:

Baseline Characteristics:

	Intervention (N =)	**Control (N =)**
Age		
Sex (% male and female)		
Classification criteria		
Duration of disease		
Treatment history		
Presence of co-morbidity		
Presence of peripheral disease		
Lost to follow up		

Other important baseline characteristics (add as necessary):

Pre -Treatment Group Differences:

Appendix 5: Detailed data extraction form for RCTs

Page 3

Data Extraction Form Page **3** of **4**

Results:
Trial primary outcomes:

Trial secondary outcomes:

See Excel spreadsheet for results

Comments on results:

Adverse events: see excel spreadsheet

Adverse Events: Described ☐ Yes ☐ No

If Yes ☐ Patient Specific ☐ Overall Statistic

Comments:

Withdrawals due to adverse events: see excel spreadsheet

Comments:

Outcomes measured at other time intervals? ☐ No ☐ Yes If yes, specify ___ days

Outcomes for Patient Subgroups:

Specify subgroups:

Appendix 5: Detailed data extraction form for RCTs

Page 4

Outcomes for patient subgroups: see excel spreadsheet

Is a letter to the author necessary for additional information?

( ) yes
( ) no

Details needed:

Appendix 6: Risk of Bias form for RCTs

RISK OF BIAS

Trial ID: ……..

Outcome: ……

DOMAIN	JUDGEMENT (YES, NO, UNCLEAR)	REASON FOR JUDGEMENT (copy and paste directly from text of trial)
Was the allocation sequence adequately generated?		
Was allocation adequately concealed?		
Was knowledge of the allocated interventions adequately prevented during the study?		
A. Blinding of personnel		
B. Blinding of participants		
C. Blinding of outcome assessors		
Were incomplete outcome data adequately addressed?		
Are reports of the study free of suggestion of selective outcome reporting		
Was the study apparently free of other problems that could put it at a risk of bias?		

Reviewer Name: ……

Appendix 7: Characteristics of included studies

Characteristics of the Study: Buchbinder 2009

Methods	Randomized Controlled Trial - Parallel Group
Participants	78 patients recruited. 38 for intervention group and 40 for control group. **Inclusion Criteria:** 1. presence of back pain of no more than 12 months' duration and 2. 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. (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. 3. edema, a fracture line, or both within the vertebral body on magnetic resonance imaging (MRI) which indicates an acute fracture **Exclusion Criteria:** 1. presence of more than two recent vertebral fractures, 2. spinal cancer, 3. neurologic complications, 4. osteoporotic vertebral collapse of greater than 90%, 5. fracture through or destruction of the posterior wall, retropulsed bony fragment or bony fragments impinging on the spinal cord, 6. medical conditions that would make the patient ineligible for emergency decompressive surgery if needed, 7. previous vertebroplasty, 8. inability to give informed consent, and 9. a likelihood of noncompliance with follow-up.
Interventions	Percutaneous vertebroplasty in the intervention group and sham procedure in the control group. According to the report, the interventional radiologists were experienced and adhered to standardized protocol but it is not clear how many radiologists were involved. **For Intervention Group:** • 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. • PMMA (approximately 3 ml.) was slowly injected into the vertebral body, and satisfactory infiltration of the vertebral body was confirmed radiographically. A bi pedicular approach was used only if there was inadequate instillation of cement with the uni pedicular 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. • After the intervention, all participants received usual care. **For Control Group:** • (Sham procedure) Patients in the control group, 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. **In Both Groups:** • 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
Outcomes	Outcomes were reported at 1 wk, 1, 3, & 6 months • The primary outcome was the score for overall pain (over the course of the previous week). The focus of this report is the primary outcome pain at 3 month. Scores for pain at rest and pain in bed at night (on a scale of 0 to 10, with higher scores indicating more pain. 10 indicating the maximum imaginable pain, and 1.5 as the minimal clinically important difference). • Trial secondary outcomes:Other outcome measures were 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; AQoL: utility measure; Roland-Morris Disability Questionnaire (RDQ): disease-specific/ modified 23-item version; EQ5D utility measure In this review we extracted overall pain, disability as measured by the RDQ, and quality of life by the EQ5D.
Source of funding	The study was 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.
Notes	The baseline characteristics of the participants were similar in the two groups. Baseline interview looks as if it was done in-person; all follow-up measures were mailed questionnaires.

Risk of bias table: Buchbinder 2009

Item	Judgement	Description
Adequate sequence generation?	Yes	On Page 559: "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)".
Allocation concealment?	Yes	Allocation occurred just prior to PV or sham procedure using opaque envelopes.
Blinding?	Yes	Blinding of personnel: With the exception of the radiologist doing the procedure. Apparently this person does not do any outcomes assessment. Blinding of participants: On Page 559: "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". Would assume that patients were blinded during follow-up since mailed questionnaires were used. Blinding of outcome assessors: On Page 559: "Baseline data, which were collected by a blinded assessor". All participants were evaluated with the use of mailed questionnaires at 1 week and 1, 3, and 6 months after the procedure.
Incomplete outcome data addressed?	Yes	Lost to follow-up was 3 of 38 in the intervention group and 4 of 40 in the treatment group. 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.
Free of selective reporting?	Yes	All outcomes planned in the published protocol are reported. Results beyond 6 months follow-up are expected to be published as this is an ongoing trial. Loss to follow-up was less than 10%.
Free of other bias?	Yes	However clarification is needed for assessing the referral bias; inadequate data on the 4 referring centres.

Characteristics of the Study: Kallmes 2009

Methods	Randomized Controlled Trial - Parallel Group. Multi-center. CROSSOVER: Subjects allowed to cross over at 1 month and 3 months post initial intervention. Not true crossover, more early escape. Patients were told at the time of consent that they would be allowed to cross over to the other procedure 1 month or later after the intervention if adequate pain relief was not achieved. Patients were seen in the clinic for the 1-month follow-up visit by a vertebroplasty practitioner to discuss whether to cross over to receive the alternative therapy. Subjects allowed to cross over at 1 month and 3 months post initial intervention. Not true crossover, more early escape.
Participants	131 patients recruited. 68 for intervention group and 63 for control group. This was a multi-center study with total 11 centres. There were 5 centers in USA (n= 37); 5 centers in United Kingdom (n= 51); and 1 in Australia (n=22). **Inclusion Criteria:** 1. Age of 50 years or older 2. A diagnosis of one to three painful osteoporotic vertebral compression fractures between vertebral levels T4 and L5 3. Inadequate pain relief with standard medical therapy 4. A current rating for pain intensity of at least 3 on a scale from 0 to 10 5. Fractures were to be less than 1 year old, as indicated by the duration of pain **Exclusion Criteria:** 1. Neoplasm in the target vertebral body 2. Substantial retropulsion of bony fragments 3. Concomitant hip fracture 4. Active infection 5. Uncorrectable bleeding diatheses 6. Surgery within the previous 60 days 7. Lack of access to a telephone 8. Inability to communicate in English 9. Dementia
Interventions	**For Intervention Group:** • Conscious sedation was induced and sterile preparation for surgery was performed. • Fluoroscopic guidance used, • Skin and subcutaneous tissues overlying the pedicle of the target vertebra or vertebrae infiltrated with 1% lidocaine and infiltrated the periosteum of the pedicles with 0.25% bupivacaine. • Patients were then randomly assigned to undergo either the full vertebroplasty procedure or the control intervention. • 11-gauge or 13-gauge needles were passed into the central aspect of the target vertebra or vertebrae. • Barium opacified PMMA was prepared on the bench and infused under constant lateral fluoroscopy into the vertebral body.

	• Infusion was stopped when the PMMA reached to the posterior aspect of the vertebral body or entered an extraosseous space. **For Control Group:** • Patients were prepped as above. • Verbal and physical cues, such as pressure on the patient's back, were given, and the methacrylate monomer was opened to simulate the odour associated with mixing of PMMA, but the needle was not placed and PMMA was not infused. • Both groups of patients were monitored in the supine position for 1 to 2 hours before discharge.
Outcomes	Outcomes were reported at 1 month for the primary outcomes and 3, 14, and 90 days for the secondary outcomes. **The primary outcomes were:** 1. Modified Roland-Morris Disability Questionnaire (RDQ) and 2. patients' ratings of average back-pain intensity during the preceding 24 hours (on a scale of 0 to 10, with higher scores indicating more severe pain). **Trial secondary outcomes were:** 1. Pain Frequency Index and the Pain Bothersomeness Index 2. Study of Osteoporotic Fractures-Activities of Daily Living (SOF-ADL) scale 3. European Quality of Life-5 Dimensions (EQ-5D) scale 4. Use of opioid medications 5. Physical Component Summary (PCS) and Mental Component Summary (MCS) sub scales of Medical Outcomes Study 36-Item Short- Form General Health Survey (SF-36), version 2
Source of funding	Supported by a grant (R01-AR49373) from the National Institute of Arthritis and Musculoskeletal and Skin Diseases.
Notes	It is difficult to determine baseline differences. No difference in age, fracture age or VAS pain (Table 1). Cannot tell from Table 2 whether baseline EQ5D, SF-36 (PCS), DPQ were different at baseline. We judged the deaths to be unrelated to the vertebral fractures and their treatment.

Risk of bias table: Kallmes 2009

Item	Judgement	Description
Adequate sequence generation?	Yes	On Page 573: "We used stratified, blocked randomization according to study center to achieve roughly balanced groups. The block sizes ranged from 4 to 12 patients... These assignments were generated by the data coordinating center with the use of a random-number generator".
Allocation concealment?	Yes	Allocation occurred just prior to PV or sham procedure using numbered opaque envelopes. Treatment assignments were concealed from all patients and study personnel who performed follow-up assessments for the duration of the study.
Blinding?	Yes	• Blinding of personnel: However the assignment will be revealed to the clinician in the procedure room after the subject has been sedated and has received local anesthesia. • Blinding of participants: On Page 573: "During the control intervention, verbal and physical cues, such as pressure on the patient's back, were given, and the methacrylate monomer was opened to simulate the odour associated with mixing of PMMA, but the needle was not placed and PMMA was not infused". According to Page 573 blinding during assessment and "control intervention". • Blinding of outcome assessors: The protocol specified that study-group assignments should be concealed from all patients and study personnel who performed follow-up assessments for the duration of the study. Only the study statisticians, who did not have any contact with the patients, saw unblinded data.
Incomplete outcome data addressed?	Yes	Not certain whether there is missing data for individual measures. Loss to follow-up was less than 10%.
Free of selective reporting?	Yes	All outcomes planned in the published protocol are reported.
Free of other bias?	Yes	

Characteristics of the Study: Klazen 2010

Methods	Open-label, Randomized Controlled Trial - Parallel Group. Multi-center. CROSSOVER: Subjects allowed to cross over at 1 week post initial intervention.
Participants	202 patients (101 were randomized to percutaneous vertebroplasty, and 101 to conservative treatment) were recruited from 431 patients who were eligible for randomisation. Between Oct 1, 2005, and June 30, 2008, 934 patients were screened for eligibility. All 934 patients who were 50 years of age or older, visiting the hospital for an X-ray of the thoracic and/or lumbar spine were asked to complete a short questionnaire about presence, severity, and duration of pain by a nurse practitioner. Of the initial 934, 732 were excluded (226 did not meet inclusion criteria, 229 had decrease of pain during the screening, 232 declined participation and 45 requested PV). **Inclusion Criteria:** 1. vertebral compression fracture on spine radiograph (minimum 15% height loss) 2. level of fracture at Th5 or lower; back pain for 6 weeks or less 3. visual analogue scale (VAS) score of 5 or more 4. bone oedema of vertebral fracture on MRI 5. focal tenderness at fracture level, as assessed by an internist on physical examination 6. decreased bone density (T scores ≤ 1) **Exclusion Criteria:** 1. severe cardiopulmonary comorbidity 2. untreatable coagulopathy 3. systemic or local spine infection 4. suspected underlying malignant disease 5. radicular syndrome 6. spinal-cord compression syndrome 7. contraindication for MRI
Interventions	**For Intervention Group:** • Pre-procedural work-up included: ECG, chest X ray and blood sampling. One hour prior to the procedure 2 g. Cefazolin was administered intravenously • Percutaneous vertebroplasty was performed on a single or biplane angiography system under fluoroscopic guidance • After local analgesia, two 11 or 13 gauge bone-biopsy needles were placed transpedicularly in the fractured vertebral body • Polymethylmetacrylate bone cement (Osteo-Firm, COOK Medical, Bloomington, IN, USA) was injected through bone-biopsy needles under continuous fluoroscopic monitoring to identify local cement leakage or migration into the venous system towards the lungs • When necessary, additional analgesia was used at the discretion of the treating physician • In patients who had more than one fracture with bone oedema on MRI, all vertebral bodies were treated in one or more procedures • After the procedure, a CT scan of the treated vertebral bodies was performed with 2 mm

	slices to identify cement leakage or other possible local complications **For Control Group:** • Conservative therapy mainly consisted of Optimal Pain Management (OPM) • The internist optimized the use of analgesics in ascending order: 1. Acetaminophen 2. Tramadol 3. Tramadol and Acetaminophen 4. Morphine • Non Steroid Anti Inflammatory Drugs (NSAID) prescribed when patients were intolerant for opiate-derivatives or in situations when already being used • Corrections in dose and classification of pain medication were made when necessary by the internist • In most cases physiotherapy was prescribed **For Both Groups:** All patients received osteoporosis medication, such as Bisphosphonates together with supplemental Calcium and vitamin D
Outcomes	Outcomes were reported at baseline, 1 month, and 1 year for the primary and secondary outcomes. **Primary outcome:** • Pain on VAS score ranging from 0 (no pain) to 10 (worst pain ever). Clinically significant pain relief was defined as a decrease of 3 points or more in VAS score from the baseline. • Pain-free days were defined as days with a VAS score of 3 or lower **Secondary outcomes:** • Cost-effectiveness at 1 month and 1 year. Cost effectiveness was defined as the ratio of difference in costs and difference in QALYs and the difference in pain-free days. Medical costs, time without burdensome pain, and quality adjusted survival time were recorded. The uncertainty with respect to the incremental cost-effectiveness ratio using bootstrapping. o Costs were indexed to 2008 (web appendix) and derived from hospital billing systems and costing guidelines issued by the Dutch health insurance board 20 o Quality-adjusted life-years (QALYs) were estimated with the EuroQol - 5 Dimensions (EQ-5D) questionnaire **Tertiary outcomes:** • Quality of life measured with the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) • Physical function: the Roland Morris Disability (RMD) questionnaire Standard questionnaires including additional questions about pain treatment, hospital stay,

	outpatient visits, and medical aids
Source of funding	ZonM and COOK Medical The study was sponsored by ZonMw (Dutch organisation for health care research and innovation of care), project number 945-06-351 and an unrestricted grant from the COOK Medical (Bloomington, IN, USA).

Notes	• Significant crossover
	  o 6 patients assigned to vertebroplasty did not receive the procedure because their health deteriorated before treatment (n=3) or they had spontaneous pain relief (n=3)
	  o 10 patients assigned to conservative treatment with ongoing invalidating pain requested and received vertebroplasty during follow-up
	• 6 patients who were assigned to conservative treatment and 2 patients who were assigned to vertebroplasty, withdrew and were not attended in any of the study centres, treatment choice was unknown and follow-up could not be obtained
	• 163 (81%) participants completed 1 year of follow-up
	• There were "Pre -Treatment Group Differences":
	  o EQ5-D; Lower score in vertebroplasty group (minimum clinically important difference is 0.5)
	  o QUALEFFO & RMD worse scores for vertebroplasty group

Risk of bias table: Klazen 2010

Item	Judgement	Description
Adequate sequence generation?	Yes	Patients were randomly allocated to percutaneous vertebroplasty or conservative treatment by an independent central telephone operator using computer generated randomisation codes with a block size of six.
Allocation concealment?	No	Masking was not possible for participants, physicians, and outcome assessors.
Blinding?	No	Patients were aware of treatment assignment and 10 patients who were assigned to conservative treatment with ongoing invalidating pain requested and received vertebroplasty during follow-up. The assessors were not blinded as well.
Incomplete outcome data addressed?	Unclear	Imputation plus "Last Observation Carried Forward". 10% of patients in the control group received vertebroplasty, starting at 1 week.
Free of selective reporting?	Yes	All drop outs accounted for and intention to treat analysis.
Free of other bias?	Unclear	Authors stated that "the treatment could not be masked". Knowledge of the treatment assignment might have affected patient responses to questions or radiologist assessments.

Characteristics of the Study: Rousing 2009

Methods	Randomized Controlled Trial - Parallel Group.
Participants	50 patients recruited. 26 for intervention group and 24 for control group. **Inclusion Criteria:** • Intractable pain because of either acute (<2 weeks, 40 patients) or subacute (between 2 and 8 weeks, 10 patients) • Osteoporotic fractures preventing the patient in taking care of oneself, and • Sufficient cognitive function to complete the study **Exclusion Criteria:** • Ages under 65 • Uncorrected therapeutic anticoagulation • Senile dementia, impaired cognitive function or other cerebral disease • Infection in the spine or the overlying skin • Malignant disease • Bone metabolic disease • Fracture of tubular bone • Allergy to radiopaque agents
Interventions	**For Intervention Group:** • PVP was performed in the operating theater and under local anaesthetics by orthopaedic surgeons specialized in spine surgery. Most patients were mildly conscious sedated and all patients were prepared for general anaesthetics in case of complications. • Under biplane fluoroscopic control and with the patients in a prone position 11- to 13-gauge needles were placed using a uni or bilateral transpedicular approach. • Bone cement (PMMA) was injected under continuous fluoroscopy. In case of extra vertebral cement leakage, the injection was terminated. • Monitoring during the procedure included electrocardiogram, oxygen saturation, and blood pressure. After the procedure, the patients were held in a prone position for 30 minutes and supine for further 90 minutes. **For Control Group:** • Patients were offered brace treatment • Both groups were offered pain medication and physical therapy if necessary until discharge
Outcomes	Outcomes were reported at baseline and 3 months. The primary outcomes were (Not explicitly stated but within the research hypothesis): • Pain (VAS, Dallas Pain Questionnaire)

	• Overall health (SF-36) • The secondary outcomes (The PhD-study was affiliated to the study and outcomes could be considered secondary outcomes): • EuroQol (EQ5D) • Barthel • A modified mini-mental status examination (MMSE) • 3 physical tests (TUG, tandem walking, “repeated chair stand”)
Source of funding	On Page 1349: "Foundation and Danish government funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript".
Notes	Vertebroplasties were performed at the Department of Orthopaedics by orthopaedic surgeons specialized in spine surgery. There were Significant differences in baseline pain. 1 patient died within 3 months of follow-up authors believe that it was unrelated to the vertebral fractures and their treatment. 1 patient was reported as non-compliant.

Risk of bias table: Rousing 2009

Item	Judgement	Description
Adequate sequence generation?	Yes	After inclusion the patients were randomized to either PVP or conservative treatment. Patients were assigned to 1 of the 2 treatments after opening a sealed envelope containing either the text “percutaneous vertebroplasty” or “conservative treatment.”
Allocation concealment?	Unclear	Allocation was done by opaque envelopes prepared and distributed by the investigating surgeon.
Blinding?	No	Blinding of personnel: On Page 1351: "Because of the nature of the intervention blinding was not possible". Blinding of participants: On Page 1351: "Because of the nature of the intervention blinding was not possible". Blinding of outcome assessors: Mostly self-reported outcomes. Point to consider: The physical tests were only performed at the 3-month follow-up visit. It is assumed that the assessors were no blind as compared to a mailed questionnaire.
Incomplete outcome data addressed?	Yes	In tables reported numbers for individual measures. Loss to follow-up was less than 10%.
Free of selective reporting?	Yes	Trial protocol is not published. However all major outcomes are reported in the study.
Free of other bias?	No	Not all participants had primary outcome measures at the baseline (VAS, SF-36, DPQ)6-15 patients in each group).

Characteristics of the Study: Voormolen 2007

Methods	Randomized Controlled Trial - Parallel Group CROSSOVER: The intention of the study was to follow the patients from both groups for 1 year with MR imaging scans and standardized questionnaires at serial intervals in time: 1 day, 2 weeks, and 3, 6, and 12 months after start of the study. The patients randomized in the "optimal pain medication" arm, who still had severe pain 2 weeks after initiating optimized analgesic treatment, could undergo PV if they wanted to ("crossover"). On Page 556: "Our original study design was changed during our trial. Because nearly all of the patients randomized in the OPM arm requested to be treated by PV 2 weeks after start of OPM treatment, we stopped the study early. Our interest was to compare the outcomes between the treatment arms. Consequently, the follow-up data from 2 weeks after the start of treatment were not analyzed in this study. The results from the patients who requested subsequent PV were analyzed 2 weeks after PV to compare these results with the results from the period during OPM treatment".
Participants	34 patients recruited. 18 for intervention group and 16 for control group (optimal pain medication) Patients were treated within 1 week after study enrolment. **Inclusion Criteria:** 1. VCF with height loss of the vertebral body (minimal 15%) on x-ray of the spine 2. Invalidating back pain related to the VCF refractive to medical therapy for at least 6 weeks and no longer than 6 months 3. Focal tenderness on physical examination related to the level of the VCF 4. Bone attenuation T-scores less than -2.0, 5 5. Bone marrow edema of the affected VCF on MR imaging scan of the spine 6. Patient age 50 years or older **Exclusion Criteria:** 1. Poor cardiopulmonary condition 2. Untreatable coagulopathy 3. Ongoing systemic infection or local infection of the spine (osteomyelitis, spondylo discitis) 4. Radicular and/or cord compression syndrome 5. Indication of other underlying disease than osteoporosis 6. No informed consent
Interventions	For Intervention Group: • Percutaneous vertebroplasty was performed under local anaesthesia on a biplane (n = 2 hospital departments) or monoplane (n = 1 hospital department) angiographic unit. • In most cases, a bilateral transpedicular approach was used. Under continuous fluoroscopy, PMMA bone cement (Osteopal V; Biomet Merck, Ried B. Kerzers, Switzerland) was injected manually using 1.0-mL syringes and 11- or 13-gauge bone biopsy needles (Cook Europe Bjaeverskov, Denmark).

	• Immediately after the PV, a CT scan with multiplanar reconstructions of the treated levels was performed to assess the cement deposition and to identify possible extra cement leakage or other local complications that might not have been noted under fluoroscopy. **For Intervention Group:** • We assume this is usual care. • Optimal pain medication: The pain medication was optimized according to the individual need of patients and patients were treated with one or more of the following medications: o Paracetamol (acetaminophen) o Non-steroidal anti-inflammatory drugs (NSAIDs) o Opiate derivatives • To optimize analgesic use, at first the dose per day of prescribed analgesics was regulated. Second, the class of pain medication was adjusted.
Outcomes	Outcomes were reported at 2 weeks. 1. Pain on VAS 2. Type of analgesic use (ordinal variable from 0 (no analgesic use) to 3 (use of opiate derivatives) 3. Roland-Morris Disability Questionnaire (RDQ) and 4. QUALEFFO.
Source of funding	None mentioned.
Notes	We do not know how the randomization was accomplished except that patients were "randomized".

Risk of bias table: Voormolen 2007

Item	Judgement	Description
Adequate sequence generation?	Yes	The patients were randomized in 2 groups by an independent central operator.
Allocation concealment?	No	Not mentioned.
Blinding?	No	Not mentioned.
Incomplete outcome data addressed?	No	Consequently, the follow-up data from 2 weeks after the start of treatment were not analyzed in this study. 4 patients refused to fill out questionnaires 2 weeks after treatment (essentially end of the study). Data not analyzed and no mention of which group originally assigned to.
Free of selective reporting?	Unclear	Trial protocol is not published. However all major outcomes are reported in the study. We do not know if follow-up were mail-out questionnaires or clinic visits.
Free of other bias?	No	On Page 556: "Our original study design was changed during our trial. Because nearly all of the patients randomized in the OPM arm requested to be treated by PV 2 weeks after start of OPM treatment, we stopped the study early". On Page 560: "...the small sample and short follow-up limit the findings".