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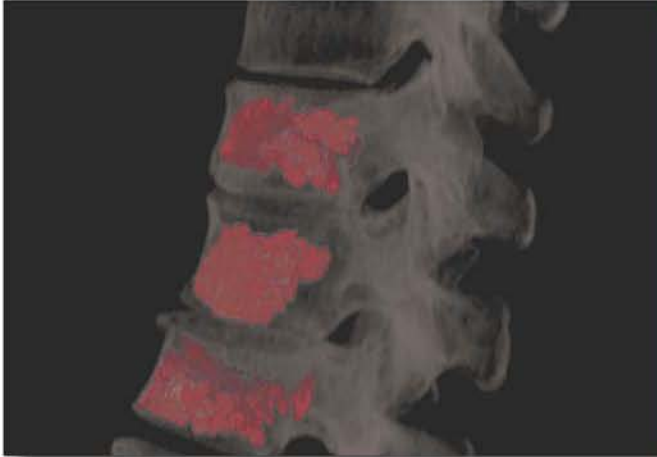
The handle <http://hdl.handle.net/1887/19836> holds various files of this Leiden University dissertation.

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Title: Percutaneous vertebroplasty for painful long-standing osteoporotic vertebral compression fractures : indication, clinical outcome, cement Leakage & classification

Date: 2012-09-20

Chapter



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**Treatment of Painful Osteoporotic
Vertebral Compression Fractures: a Brief
Review of the Evidence for Percutaneous
Vertebroplasty**

J Bone Joint Surg Br. 2011;93(9):1149-53

Abstract

122 Vertebral compression fractures are the most prevalent complication of osteoporosis and percutaneous vertebroplasty (PVP) has emerged as a promising addition to the methods of treating the debilitating pain they may cause.

Since PVP was first reported in the literature in 1987, more than 600 clinical papers have been published on the subject. Most report excellent improvements in pain relief and quality of life. However, these papers have been based mostly on uncontrolled cohort studies with a wide variety of inclusion and exclusion criteria. In 2009, two high-profile randomised controlled trials were published in the *New England Journal of Medicine*, which led care providers throughout the world to question the value of PVP. After more than two decades a number of important questions about the mechanism and the effectiveness of this procedure remain unanswered.

Osteoporotic Vertebral Compression Fractures

Osteoporosis is the most frequent cause of vertebral compression fractures (VCFs) in the elderly.¹ In 2000, over 40,000 new vertebral fractures due to primary or secondary osteoporosis were registered in The Netherlands.² With an ageing population it is expected that this number will only increase with time. The generally preferred initial treatment of patients with a symptomatic stable osteoporotic VCF without attendant neurological symptoms is conservative.³ In 85% of symptomatic patients, pain caused by these 'acute' osteoporotic fractures will settle within 12 weeks of starting conservative treatment.⁴⁻⁶ The remaining 15% with 'chronic' osteoporotic compression fractures, can fail to respond to conservative treatment, and there may be an indication for percutaneous vertebroplasty (PVP).

The effect of PVP on pain is reported to be rapid and to reach a plateau within a few days of the procedure,⁷ after which the pain scores do not change significantly over the following two years.⁸⁻¹¹ A meta-analysis of 60 studies by Eck et al¹² reported a change in the visual analogue scale (VAS) score. After PVP patients improved from a mean pre-operative VAS of 8.36 (SD 0.78) to a mean post-operative VAS of 2.86 (SD 1.09), with a mean statistically significant change in the level of pain of 5.68 (SD 1.24). After two high-profile randomised controlled trials, by Buchbinder et al¹³ and Kallmes et al,¹⁴ were published in the *New England Journal of Medicine* in 2009, care providers began to question the value of injecting cement into fractured vertebral bodies and revived discussion about the evidence for, the mechanism of and the risks involved in PVP.

Percutaneous Vertebroplasty

PVP is a procedure used to stabilise fractured vertebrae in order to relieve pain. It involves the injection of bone cement, usually polymethylmethacrylate (PMMA), and an opacifier into the inter-trabecular marrow space of a fractured vertebra. The procedure may be used for pathological compression fractures caused by osteoporosis, avascular necrosis, multiple myeloma or bone metastases.¹⁵⁻¹⁷ In general, patients are selected on the basis of the following: incapacitating pain at the level of the fracture which is unresponsive to conservative treatment;¹⁸ focal point tenderness, which increases when pressure is applied to the spinous process of the fractured vertebra;¹⁹⁻²¹ and bone marrow oedema in the fractured vertebral body on MR Imaging with fat suppression.²²⁻²⁵

The first PVP was performed by Deramond in 1984 and reported in the literature in 1987.²⁶ A paper in the *American Journal of Neuroradiology* in November 1997²⁷ describing a trial from the University of Virginia which comprised²⁹ patients followed over a period of three-years, with promising short-term outcomes, prompted a sudden increase in the number of procedures being performed.

PVP may be performed under general anaesthesia, although more commonly the patient is given a local anaesthetic at the injection site and conscious sedation. The procedure takes between 1 and 2 hours, depending on the number of vertebrae requiring treatment. After its injection into the vertebra, the cement hardens and prevents further collapse of the vertebral body, and is thought to support the micro fractures in the trabeculae.

As well as 'traditional' PVP, there is a similar procedure in which it is used in combination with an inflatable balloon tamp often referred to as kyphoplasty. This was developed in the early 1990s and gives comparable clinical outcomes.¹² The evidence for performing kyphoplasty is, however, beyond the scope of this review and therefore will not be discussed further.

According to a number of large studies, relief of symptoms and restoration of mobility are rapidly achieved in more than 80% of patients after PVP. Most of these studies are, however, of evidence level IIIB or IV.^{15,17,25,28} The rate of complications after PVP is reported to range between 1.6% and 2.8%.²⁹ The reported complications with PVP in osteoporotic VCFs, however, range from unanticipated and apparently clinically silent events to catastrophic complications and even death.^{12,30-32} Most of the clinically relevant complications are due to leakage of bone cement. Severe complications are rare and occur mainly in cases of high-volume cement leakage. Complications include cement penetration of the nerve root foramen or spinal canal resulting in radiculopathy or spinal cord compression, embolic events due to marrow fat or cement entering the circulation, misplacement of the needle, rib fractures, pneumothorax, fracture of spinous process or pedicle, subcutaneous paravertebral haematoma and infection.^{10,33-38}

Leakage of cement into the neural foramen or spinal canal can cause neurological injury.³² Furthermore, leakage, especially into the intervertebral disc, may lead to altered biomechanical stresses on the adjacent vertebral body and an increased risk of new fractures.³⁹ Leakage into the arterial or venous system has been reported to cause pulmonary embolism, cardiac perforation and cerebral cement embolism.^{40,41} Alongside these reported complications, it appears that the prevalence of new fractures in PVP-treated patients is between 12% and

more than 50%.^{39,42–48} Research on the development of new compression fractures after PVP has been conducted in biomechanical models and clinical trials.^{48–50} Up to 70% of new fractures after PVP are adjacent to a previously treated level.^{47,51} The main difficulty in conducting clinical trials to answer the question ‘Does PVP increase the risk of subsequent fracture of the adjacent vertebral body?’ is that in a patient who has already sustained one compression fracture the risk of developing a new fracture is increased, whether the previous fracture has been treated or not.^{52–54} Biomechanical testing may explain why secondary adjacent fractures occur in patients with a wedge compression fracture, as the mechanical load on the endplate changes from perpendicular to a shearing off-axis load.⁵⁵

The exact mechanism of pain relief by cement augmentation of the vertebral body is still debated; it has been suggested that bone cement stops vertebral micro- or macromovement and is consequently responsible for the analgesic effect of the procedure.⁵⁶ However, there appears to be no correlation, in terms of pain relief or the use of medication, between the degree of cement filling of the fractured vertebral body and the clinical outcome.⁵⁷ Due to its rapid analgesic effects, high effectiveness, low complication rate and relatively low cost, over the past two decades PVP has become a widely used, minimally invasive treatment for painful vertebral compression fractures, despite the unknown mechanism of pain relief and the lack of studies with a high level of evidence.

Uncontrolled Clinical Vertebroplasty Trials (Level IV Evidence)

Since 1987 more than 600 clinical papers about PVP have been published. The largest trials to date are those conducted by McGraw et al¹⁵ (100 patients), Evans et al⁵⁸ (245 patients), Kobayashi et al²⁸ (175 patients), Alvarez et al²⁵ (278 patients), Layton et al¹⁰ (552 patients) and Masala et al¹¹ (624 patients), which were mostly non-randomised and retrospective. They report markedly different patient selection criteria, duration of follow-up and outcome measures, but uniformly encouraging results for short-term pain relief in the vast majority of patients. The study by Masala et al¹¹ also showed that the significant mean reduction in pain achieved (6.5 points on a VAS) four hours after the procedure was unchanged one year later. However, without any form of concurrent or historical control group it is impossible to be confident of the true benefits of PVP. Some or all of the improvement might be caused by the favourable natural course of an osteoporotic VCF,⁶ or by a placebo effect.⁵⁹

Non-Randomised Controlled Clinical Vertebroplasty Trials (Level III B Evidence)

In 2003, Diamond, Champion and Clark⁶⁰ conducted the first non-randomised controlled trial of PVP against conservative treatment in 79 patients. This study showed a significant and immediate effect on pain relief, with improved function and reduced use of analgesics after 24 hours. However, it also showed that the effect might be short-lived. Substantial improvements seen in the conservatively treated group resulted in there being no clinically important differences between the two treatment groups in pain or function at six weeks or between six and 12 months.^{54,60} The lack of randomisation in this study raised the possibility of selection bias, although both groups of patients had similar characteristics before treatment. Furthermore, without blinding the patient to the treatment received, it is impossible to disentangle the treatment effect from the placebo effect.

Randomised Controlled Clinical Vertebroplasty Trials (Level IIB Evidence)

In 2002, Do et al⁶¹ randomly assigned 31 patients with acute VCFs to PVP or continued medical treatment. This study suggested improvements in pain, activity and analgesic use six weeks after intervention.

In 2007, Voormolen et al⁹ compared PVP with optimal pain medication (OPM) in the VERTOS I study. They reviewed 34 patients who had suffered from painful osteoporotic VCFs for more than six weeks but no longer than six months, and randomised them to PVP or OPM. As nearly all of the patients randomised to the OPM group requested to cross over after two weeks, the study was stopped early. This suggested that pain relief, improved mobility, function and stature after PVP are immediate and significantly better in the short term than following OPM treatment.⁹ To gain more insight into the cost-effectiveness of PVP, a second trial (VERTOS II) was conducted by Klazen et al^{62,63}: the results were published in *The Lancet* in 2010. In this trial, 202 patients with back pain lasting for six weeks or less as a result of an osteoporotic VCF were randomly allocated to PVP or conservative treatment. Inclusion criteria included focal tenderness over a compression fracture with a minimum of 15% loss of vertebral height, osteoporosis, and bone marrow oedema on MR Imaging. The primary outcome was the relief of pain after one month and one year using a VAS. This showed that vertebroplasty resulted in greater pain relief than conservative treatment. The authors concluded that pain relief after vertebroplasty is

immediate, is sustained for at least a year, and is significantly greater than that achieved with conservative treatment.⁶²

Randomised Controlled Blinded Vertebroplasty Trials (Level IB Evidence)

A number of authors have emphasised the importance of randomised blinded controlled trials of PVP in order to obtain level I evidence.^{56,59,60,64,65} So far, three such trials have been conducted. In 2002, Kallmes et al⁶⁶ conducted a small, single-blinded, randomised crossover study in which five patients with subacute vertebral fractures were included. The control procedure involved the injection of local anaesthetic next to the vertebral body, without introducing cement. Three patients initially underwent the control procedure and two underwent PVP. All patients in both groups had minimal relief of symptoms and chose to cross over to the other procedure. All patients guessed that they had received the control procedure first.⁶⁶ However, this pilot study demonstrated the feasibility of enrolling patients into a sham-controlled trial of PVP.⁶⁵

In 2009, two randomised, blinded controlled trials were published. The INvestigational Vertebroplasty Efficacy and Safety Trial (INVEST) conducted by Kallmes et al¹⁴ randomised patients to PVP versus a control intervention in which local anaesthetic was injected without cement.⁶⁷ Both the patients and the clinical coordinators who performed the follow-up remained blinded to the type of procedure. The primary outcomes were pain relief and Roland Morris Disability Scale score⁶⁸ at 30 days. Patients were followed clinically for one year.

The second randomised blinded trial by Buchbinder et al¹³ offers some potential advantages over the INVEST trial. First, in control patients a PVP needle was placed into the bone, but without the injection of cement, whereas in the INVEST trial a PVP needle was not placed in bone. This difference in design might have made it easier to blind patients to the type of procedure. Secondly, crossover was not allowed in the trial by Buchbinder, which allowed longer-term follow-up than was possible in the INVEST trial.

Both the INVEST trial and the trial conducted by Buchbinder found that pain was significantly reduced after PVP, but that the improvement was not clinically more significant than that in the control groups. The overall conclusion of the INVEST trial was that at one month the clinical improvement in patients with painful osteoporotic VCFs was similar in those treated with PVP and those treated with a simulated procedure. The overall conclusion of the trial

by Buchbinder also showed no beneficial effect of PVP over a sham procedure after one week, or at one, three or six months, among patients with painful osteoporotic VCFs.

Because both papers were published simultaneously in the *New England Journal of Medicine*,^{13,14} the results had a major effect on physicians, the media and the public, and a procedure which had shown very promising results in numerous large cohort studies was instantly discarded by many. The high-profile nature of the articles makes this rigorous step understandable but not necessarily justifiable. Even though these studies may be the only two blinded randomised controlled trials of reasonable size, some important considerations should be considered when reading these papers.

In both studies the inclusion criteria were not the generally accepted indications for PVP, which are focal back pain on palpation corresponding to a fracture, and bone marrow oedema on MRI.^{8,24,25} In both studies physical examination was disregarded, potentially leading to the inclusion of other causes of back pain. Furthermore, the study by Kallmes¹⁴ lacks the standard inclusion criteria of bone marrow oedema, and in both studies only one-third of eligible patients without contraindications were included, and with these numbers a selection bias is highly likely.

In the study populations of both the INVEST¹⁴ and in the study by Buchbinder¹³ a high percentage of patients suffered from acute fractures (less than six weeks old). In the INVEST study 32% of the fractures were acute. In the Buchbinder study 44% of the fractures were of mixed age, ranging from one to 14 weeks old. Subgroup analysis did not demonstrate statistically significant differences between chronic and subchronic fractures because of the small numbers available. In the study populations described by Buchbinder¹³ and Kallmes,¹⁴ patients with pseudoarthroses after an osteoporotic VCF, which are known to not respond well to conservative treatment,⁶⁹ were entirely missing. A reduction in VAS of 3 to 6 points one week after PVP is common in the literature.¹² The INVEST study showed values close to this range, with 2.3 points at day three to 2.9 points at day 14. Remarkably, the opposite results are shown by the trial by Buchbinder, a 1.5 reduction in VAS after PVP being among the smallest in literature and barely clinically relevant.⁷⁰

Furthermore, by presenting short-term results in both studies, the natural course is not taken into account,⁴ which results in a lack of statistical power to draw any long-term conclusions.

Conclusions

Indisputable level 1 evidence in favour for or against the effectiveness PVP is still lacking. The most probable explanation for the positive effects observed in prospective cohort studies still seems to be the mechanical impact of the bone cement. Until proven, however, this will continue to be a hypothesis. The randomised, but effectively unblinded, trials conducted by Voormolen et al⁹ and Klazen et al⁶² are well designed and use clear, widely used inclusion criteria, such as focal tenderness on physical examination and bone marrow oedema on MRI scan. The studies give some answers to the question 'Is PVP better than continuing conservative treatment for a longer period?' and suggest that pain relief after PVP is immediate, is sustained for at least a year, and is significantly greater than that achieved with conservative treatment.

The randomised, double-blind controlled INVEST¹⁴ trial and the trial by Buchbinder¹³ were conducted with far less clear inclusion criteria, in which physical examination and MRI had a limited or no role in the standard work-up. We feel that the trials by Buchbinder¹³ and Kallmes¹⁴ have made it easier to discuss placebo-controlled vertebroplasty trials with medical ethical committees. Because of these publications it is clear that a well-designed double-blinded randomised controlled trial using the right indications and inclusion criteria is feasible and should be performed in the near future.

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