Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for the treatment of osteoporotic vertebral fractures: a systematic review and cost-effectiveness analysis

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Scientific summary

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Scientific summary

Background

Osteoporosis is a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a resulting increase in bone fragility and susceptibility to fracture. The clinical significance of osteoporosis lies not in low bone mass per se but in the fractures that may occur as a consequence. In vertebral fracture, one or more vertebrae are compressed, leading to a reduction in height and potentially also to abnormal curvature of the spine (kyphosis). Vertebral compression fractures (VCFs) can lead to severe acute and chronic pain, impaired mobility and reduced quality of life. They have also been linked to poor cardiopulmonary function and appetite, and an increased risk of mortality. Although VCFs are thought to be common, it is difficult to give a precise estimate of prevalence and incidence as the majority remain undiagnosed. When painful VCFs do come to clinical attention, they are typically treated with optimal pain management (OPM) consisting of analgesics, bed rest and back bracing. However, this approach is unsatisfactory for a proportion of patients and, when used as a longer-term treatment, can lead to exacerbation of the underlying osteoporosis.

Percutaneous vertebroplasty (PVP) is a minimally invasive surgical procedure in which bone cement (such as polymethylmethacrylate, glass polymers, hydroxyapatite and calcium phosphate) is injected into a fractured vertebra under radiological guidance using fluoroscopy. The procedure is usually performed under intravenous sedation or light general anaesthesia. A disposable bone biopsy needle or trocar needle is placed centrally in the vertebral body using an image-guided safe access route. This may be done bilaterally through the pedicles, oblique across one pedicle or lateral oblique through the base of the pedicle. The cement is then injected very slowly, again under constant fluoroscopic guidance. Percutaneous balloon kyphoplasty (BKP) is a variation of this approach, in which an inflatable balloon tamp is placed in the collapsed vertebra prior to cement injection in order to create a cavity allowing low pressure injection. A potential advantage of kyphoplasty is that it may partially correct the reduction in vertebral height; however, the degree of height restoration may be none or minimal. Early case reports, retrospective case series and quasi-experimental studies suggested that these procedures led to dramatic improvements in pain and physical functioning. Furthermore, there are plausible biomechanical reasons that may account for these improvements, such as stabilisation of the collapsed vertebra, correction of kyphotic deformity and height restoration. However, two recent double-blind, operative placebo with local anaesthetic (OPLA) controlled trials of PVP suggest that the procedure may provide no greater benefits than administration of local anaesthetic to the affected area.

Objectives

The objective of this review was to systematically evaluate and appraise the clinical effectiveness and cost-effectiveness of PVP and BKP in reducing pain and disability in people with osteoporotic VCFs in England and Wales. The study also included a narrative review of safety.

Methods

A systematic search of databases including MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, EconLit, The Cochrane Library, and Database of Abstracts of Reviews of Effects (DARE) was conducted with a cut-off date of November 2011. Search terms included ‘vertebroplasty’, ‘kyphoplasty’, and a broad variety of related clinical terms. Studies met the inclusion criteria if they were randomised controlled trials (RCTs) including people of any age and either sex with

painful osteoporotic vertebral compression fractures. The intervention groups of these trials must have received PVP or BKP, and the comparators were the interventions themselves, conservative management, or defined as sham surgery. Primary outcomes were health-related quality of life, back-specific functional status/mobility, pain/analgesic use, vertebral body height and angular deformity, incidence of new vertebral fractures, and progression of treated fracture. Safety was assessed in a narrative review including data from the RCTs of PVP and BKP along with large case series ($\geq$ 200) and individual case reports of complications.

Data were extracted independently by two reviewers using a standardised data extraction form; discrepancies were resolved by discussion. The quality of the included studies was critically assessed by the same two reviewers using a tool based on the criteria proposed by the Centre for Reviews and Dissemination and the Cochrane Collaboration for assessing the risk of bias in randomised trials, and also including some vertebral augmentation-specific items.

Owing to the potential impact of baseline imbalances in the degree of pain and disability reported by patients with osteoporotic VCFs, outcomes that were reported as continuous data were assessed in terms of the difference between the mean changes from baseline in the intervention and control groups, rather than absolute differences at any time point. For dichotomous outcomes, relative risks, with confidence intervals and *p*-values, were calculated using The Cochrane Collaboration's Review Manager software (version 5.1, The Nordic Cochrane Centre, Copenhagen, Denmark) if such data were not reported by the study investigators. Where appropriate, a meta-analysis was carried out with random effects models, using Review Manager. However, such meta-analysis was limited to dichotomous outcomes. It was not considered appropriate to undertake a meta-analysis of continuous or quasi-continuous outcomes because a previous meta-analysis of individual patient data from the two double-blind OPLA-controlled trials has already been published. Where meta-analysis was not possible, published data were tabulated and discussed in a narrative review.

Medtronic provided observational data indicating that vertebral augmentation may be associated with a beneficial mortality effect, and that potentially BKP was more efficacious than PVP. The clinical hypothesis for this effect is that as patients become more mobile more quickly, the (typically elderly) patients are less prone to infection. These data were formally critiqued.

A mathematical model was constructed to explore the cost-effectiveness of BKP, PVP (using low-viscosity cement in 85% of patients and high-viscosity cement in 15% of patients) and OPLA compared with OPM. Owing to uncertainty in the evidence base, six scenario analyses were conducted that assessed combinations of assumptions on mortality (differential beneficial effects for BKP and PVP; equal beneficial effects for BKP and PVP; and no effect assumed) and derivation of utility data [either solely mapped from visual analogue scale (VAS) pain score data produced by a network meta-analysis or using direct European Quality of Life-5 Dimensions (EQ-5D) data from the trials]. Extensive sensitivity analyses were conducted on each of the six scenarios. Exploratory analyses were conducted on the cost-effectiveness of using high-viscosity cement in all patients, on the available costs for patient education to obtain the OPLA response while maintaining a cost per quality-adjusted life-year (QALY) gained ratio below £20,000 and on the use of initial facet joint injections.

Results

Number and quality of studies

Twenty-eight articles relating to a total of nine RCTs were identified and included in the review of clinical effectiveness. This body of literature was of variable quality, with the two double-blind, OPLA-controlled trials [Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt C, *et al.* A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med* 2009;**361**:557–68; Gray LA, Jarvik JG, Heagerty PJ, Hollingworth W, Stout L, Comstock BA, *et al.* INvestigational Vertebroplasty Efficacy and

Safety Trial (INVEST): a randomized controlled trial of percutaneous vertebroplasty. *BMC Musculoskeletal Disord* 2007;**8**:126] being at the least risk of bias. The most significant methodological issue among the remaining trials was lack of blinding for both study participants and outcome assessors. In addition, only the two OPLA-controlled trials provided adequate information on the prior training, skills and knowledge of the operators.

Summary of benefits and risks

Broadly speaking, the literature suggests that both PVP and BKP provide substantially greater benefits than OPM in open-label trials. However, in double-blinded trials PVP was shown to have no more benefit than local anaesthetic; no trials of BKP compared with local anaesthesia have been conducted.

Quality of life was most often assessed with the EQ-5D and/or the Quality of Life Questionnaire of the European Foundation for Osteoporosis scales. Findings indicated greater improvements on both these measures in the open-label trials of PVP [Blasco JA, Martinez-Ferrer A, Macho Fernández J, San Roman Manzanera L, Pomés Talló J, Carrasco Jordan JLl, *et al.* Effect of vertebroplasty on pain relief, quality of life and the incidence of new vertebral fractures. A 12-month randomised follow-up, controlled trial (published online ahead of print 3 February 2012). *J Bone Miner Res* 2012. doi:10.1002/jbmr.1564; Rousing R, Andersen MO, Jespersen SM, Thomsen K, Lauritsen J. Percutaneous vertebroplasty compared to conservative treatment in patients with painful acute or subacute osteoporotic vertebral fractures. Three-months follow-up in a clinical randomized study. *Spine* 2009;**34**:1349–54; Farrokhi MR, Alibai E, Maghami Z. Randomized controlled trial of percutaneous vertebroplasty versus optimal medical management for the relief of pain and disability in acute osteoporotic vertebral compression fractures. *J Neurosurg Spine* 2011;**14**:561–9; Voormolen MHJ, Mali WPTM, Lohle PNM, Fransen H, Lampmann LEH, van der Graaf Y, *et al.* Percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures. The VERTOS study. *Am J Neuroradiol* 2007;**28**:555–60; and Klazen CAH, Lohle PNM, Jansen FH, Tielbeek AV, Blonk MC, Venmans A, *et al.* Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial. *Lancet* 2010;**376**:1085–92]; however, no differences in quality of life were observed in either of the OPLA-controlled, double-blind trials (Buchbinder and INVEST). Four open-label studies [Farrokhi, Rousing, VERTOS II and Wardlaw D, Cummings SR, Van Meirhaeghe J, Bastian L, Tillman JB, Ranstam J, *et al.* Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. *Lancet* 2009;**373**:1016–24] found significantly greater improvements in pain among the operated cohorts, while the double-blind trials found no or a small non-significant benefit. Although there was a trend towards greater pain reduction in the PVP group in one of these OPLA-controlled trials (the INVEST study), this may have been confounded by a higher level of opioid use among the PVP group. With respect to analgesic use, also, there were greater reductions among non-operated patients in the open-label trials, while no significant between-group differences were seen in the double-blind trials. In a head-to-head trial of PVP and BKP (Liu JT, Liao WJ, Tan WC, Lee JK, Liu CH, Chen YH, *et al.* Balloon kyphoplasty versus vertebroplasty for treatment of osteoporotic vertebral compression fracture: a prospective, comparative, and randomized clinical study. *Osteoporos Int* 2010;**21**:359–64), VAS pain scores did not differ significantly between the treatment groups.

There were no data on restoration of vertebral body height or kyphotic wedge angle that could be compared between studies. However, the one trial that undertook a comparison of PVP and BKP (Liu) suggests that BKP may be the more effective method. Only one study comparing BKP with OPM was identified (FREE). This suggested that BKP is more effective for reducing pain, and improving back-related functional ability and quality of life. However, the methodological limitations of this study – most notably lack of blinding and unexpected imbalances in dropout – made it difficult to draw inferences with any confidence.

Known complications of PVP and BKP include pulmonary embolism, periprocedural hypotension, radiculopathy, damage to surrounding tissue, paraparesia, paraplegia, rib fracture and postoperative

infection. Most of these complications are associated with the leakage of bone cement outside the treated vertebra. Although intradiscal leakage is unlikely to lead to complications, epidural leakage can have serious consequences, and a number of procedure-related deaths have been reported. Incidence of serious complications is rare, but the long-term implications of clinically silent cement leakages and pulmonary emboli remain poorly understood.

A meta-analysis of mortality rates suggested that PVP might be associated with reductions in mortality. However, this effect failed to reach statistical significance and the included trials were not designed to detect this outcome. A formal analysis of mortality data undertaken within this report concludes that it is possible that there is a causal difference in mortality between patients treated using OPM and patients receiving BKP or PVP given the size of the effect. Appropriately taking into account the potential endogeneity of the treatment would tend to reduce the point estimate of the effect size but may or may not eliminate it completely. It is not possible to say with certainty if there is a difference in mortality between patients undergoing BKP and PVP owing to the treatment based on the data presented. There is also considerable uncertainty, were BKP and PVP assumed to have a mortality benefit, as to whether or not OPLA would also produce a mortality benefit.

The cost-effectiveness ratios of the interventions were driven by the scenario chosen. If a differential mortality effect was chosen, then BKP consistently had a cost-per-QALY-gained ratio below £20,000. If a pooled beneficial effect was used then PVP consistently had a cost-per-QALY-gained ratio below £10,000. Where no mortality effect was assumed then the derivation of utility influenced the results. Using the EQ-5D values mapped from VAS pain scores produced by a network meta-analysis, PVP typically was the dominant intervention or had a cost-per-QALY-gained ratio below £15,000 with the exception of when a number of parameters were altered that did not favour PVP. When data from the two high-quality blinded trials (Buchbinder *et al.* and INVEST) were used then the cost-per-QALY-gained ratios for PVP and BKP were often greater than £20,000, depending on the other assumptions made.

The exploratory analyses indicated that the use of high-viscosity cement in all patients was unlikely to have a cost-per-QALY-gained value below £20,000, that sums in excess of £500 (and potentially considerably more) per patient could be spent to achieve the OPLA response rather than undertake PVP and that an initial facet joint injection prior to vertebral augmentation appeared a sensible option.

Discussion

Strengths, limitations of the analyses and uncertainties

To our knowledge, this is the first systematic review to undertake a comprehensive clinical effectiveness and cost-effectiveness analysis of PVP and BKP for the treatment of osteoporotic VCFs. The clinical effectiveness analysis included RCTs only, and provided an overview of the complications that may arise from these procedures. However, the internal validity of the included literature was compromised by widespread lack of blinding. To date, there has been only one open-label trial that has compared BKP with conservative management, and so the effectiveness of this procedure was particularly difficult to establish. The use of subjective ratings of pain as an outcome measure may be confounded by various psychosocial and patient-level factors. Important questions that are yet to be convincingly addressed include the effect of vertebral augmentation on mortality and on correction of vertebral body height and kyphotic deformity. The analyses conducted the most robust mapping of VAS to EQ-5D of which we are aware, and undertook a network meta-analysis of the VAS data. Extensive scenario and sensitivity analyses were conducted to explore a wide range of different assumptions. Insufficient evidence, particularly on the impact of BKP, PVP and OPLA on mortality rates, means that no definitive conclusion can be made.

Generalisability of the findings

This review was specific to the population of people with painful osteoporotic VCFs; hence, the results are not necessarily generalisable to VCFs of other origins (e.g. multiple myeloma, traumatic, metastatic

deposits). Most studies did not present data on the ethnic composition of their samples or discuss the implications of this for generalisability. Furthermore, the procedures reported in those studies were usually performed by experienced personnel, and therefore their results may differ from those obtained by less experienced practitioners. On the other hand, the age and sex make-up of the study samples was fairly representative of the wider population of people with osteoporotic VCFs. A higher proportion of females took part in the trials (typically around 70%) and the mean sample age was usually early to mid-70s.

Conclusions

For people with painful osteoporotic VCFs refractory to analgesic treatment, PVP and BKP perform significantly better in unblinded trials than OPM in terms of improving quality of life and reducing pain and disability. However, there is as yet no convincing evidence that either procedure performs better than OPLA with data from two high-quality trials (Buchbinder and INVEST). It can be argued that these procedures should not be undertaken unless the patient has failed to respond to a facet joint injection.

It is possible that BKP and PVP may lead to reductions in mortality and at different levels of effect; however, this possibility was derived from registry data and without information on the causes of death in these cohorts, and in the absence of randomisation, it was not possible to conclusively establish a causal link. There were no data to analyse whether or not OPLA would also be associated with mortality benefits. If such benefits exist then the cost per QALY gained of the interventions compared with OPM would be low.

Although complications associated with PVP and BKP are rare, they can be serious, and procedure-related deaths have been reported.

Suggested research priorities

- There is yet to be a double-blind, placebo-controlled trial of BKP. A well-designed study comparing BKP with OPLA should be considered.
- There are questions as to whether or not postoperative pain and quality of life improvements from PVP and BKP arise from a placebo response or the specific efficacy of the procedures. It may be that the failure of PVP to demonstrate greater benefits than OPLA suggests placebo efficacy only. Alternatively, it may be that the infusion of local anaesthetic has specific mechanisms of efficacy over conservative treatment. RCTs comparing local anaesthesia with OPM, and multiarm RCTs comparing vertebral augmentation, local anaesthesia, facet joint injection, patient education and OPM, would provide useful data.
- The effect of vertebral augmentation on mortality is an important yet inadequately understood issue. Large-scale registry data from Germany and the USA suggest that people with osteoporotic VCFs who have received augmentation have significantly improved survival rates; however, a definitive causal link could not be established. The effect of augmentation on mortality, and the impact of various extraneous variables, should be investigated through further retrospective case series with more details on causes of death. Ideally, this outcome would be explored in a well-controlled RCT. However, the sample size and length of follow-up required to detect meaningful differences would make such a trial difficult to perform.
- The length of stay associated with patients receiving OPM, PVP and BKP is not known with certainty, with the pivotal trials suggesting that the length of stay is considerably shorter than hospital database values. A prospective study to record such values would be beneficial.
- Sagittal balance and spinal deformity have a substantial impact on quality of life and fracture-related disability. However, the effectiveness of PVP and BKP in restoring these morphometric parameters is yet to be studied in high-quality studies.

Study registration

The study is registered as PROSPERO number CRD42011001822.

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