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REVIEW

What is the role of vertebral augmentation for osteoporotic fractures? A review of the recent literature

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Abstract

Purpose Vertebral augmentation procedures such as vertebroplasty and kyphoplasty are utilized in the treatment of vertebral compression fractures (VCFs). However, their capacity for providing analgesia, reducing disability, and improving quality of life in patients with osteoporotic VCFs remains a topic of debate. The objective of this narrative review is to summarize the latest evidence for the safety and efficacy of vertebral augmentation for osteoporotic vertebral compression fractures (VCFs).

Methods A systematic literature search was conducted using the PubMed and Cochrane electronic databases for systematic reviews, review articles, meta-analyses, and randomized clinical trials prior to May 2017. The keywords were "vertebroplasty," "kyphoplasty," and "vertebral augmentation."

Results Thirty-three papers (7 systematic reviews, 6 cohort studies, 15 randomized clinical trials, and 5 international guidelines) were included in this narrative review.

Conclusion Vertebral augmentation is a safe procedure, with low rates of serious complications and no increase in subsequent post-treatment fracture risk.

Keywords Vertebral augmentation · Vertebroplasty · Kyphoplasty · Osteoporosis · Vertebral fracture

Introduction

Osteoporosis is a common condition in the elderly population [1, 2] and represents an important cause of pathological fracture. Of these, vertebral compression fractures (VCFs) account for around one quarter of osteoporotic fractures and constitute a major source of morbidity and increased mortality [3]. Many osteoporotic VCFs are asymptomatic or result in only minimal symptoms, with pain generally subsiding over 6 to 8 weeks, while the fracture heals. For these patients, conservative medical management, consisting of bed rest, analgesia, physical therapy, and osteoporosis medications, is the primary mode of treatment. However, in patients with more severe pain and disability, this treatment option may not only be ineffective in controlling symptoms, but also may lead to significant negative effects and increase both direct and indirect healthcare costs [4–6]. Immobilization through bed rest can lead to bone loss after 2 days [7]. Fifteen percent of aerobic capacity and lower-extremity strength may be lost after as few as 10 days bed rest [8]. The addition of narcotic analgesics, with their associated adverse effects of sedation, confusion, and constipation, may further complicate management.

For this cohort of patients, vertebral augmentation techniques may be considered [6, 9, 10]. These minimally invasive techniques involve the percutaneous injection of polymethylmethacrylate (PMMA) cement into the VCF [11,

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12]. Percutaneous kyphoplasty (PKP) involves an additional step in which a cavity is created within the vertebral body through the inflation of a balloon tamp, into which cement is injected [13].

Our aim in this narrative review is to assess the safety and efficacy of PVP and PKP for reducing pain and disability for patients with osteoporotic VCFs.

Method

A search was carried out for English-language articles (abstract and/or full-text) on PubMed and the Cochrane database. The search sequence submitted included the following keywords, combined with appropriate Boolean connectors: "vertebroplasty," "kyphoplasty," and "vertebral augmentation." We included systematic reviews, review articles, meta-analyses, and randomized clinical trials (RCTs), published up to May 2017. To increase the inclusiveness of our search strategy, we also referred to texts to find other relevant cited manuscripts not retrieved in the initial search. Given the narrative nature of this review, no formal quality assessment was done.

Results

The search of PubMed and Cochrane databases produced a total of 4545 articles. We excluded non-English papers, duplicates, case reports, non-randomized case series, comments, letters, articles reporting on outcomes for indications other than osteoporotic VCFs, and studies with inappropriate data or comparisons. Thirty-three papers were included in this narrative review: 15 randomized controlled trials, 7 systematic reviews, 6 retrospective and prospective cohort studies, and 5 international guidelines (Fig. 1).

Efficacy

A large pooled analysis of PVP for osteoporotic VCFs from 1989 to 2004 by Hochmuth et al. included 2086 patients from 30 studies [14]. Nineteen studies (63%) reported rapid and sustained pain relief after vertebroplasty, with mean pre-treatment VAS (Visual Analogue Scale) of 8.1 reduced to 2.6 ($p < 0.001$). These outcomes were attributed by multiple studies within the analysis to the role of cement in mechanical vertebral fracture stabilization and to the direct action of PMMA on nerve endings. PVP also led to improved vertebral alignment, with increased vertebral height and reduced kyphosis [14]. This promising data led to increased uptake of vertebroplasty as a treatment for painful osteoporotic VCFs. However, there remained a lack of robust data from RCTs that could evaluate the efficacy of vertebroplasty over conservative management.

The 2007 VERTOS trial was the first multicenter, open-label, prospective RCT comparing PVP to medical management for osteoporotic VCFs [15]. Inclusion criteria utilized were age < 50 years, severe pain, fractures aged 6–24 weeks, bone marrow edema on MRI, and tenderness on spinal examination. In total, 34 patients were randomized to receive either PVP ($n = 18$) or best medical management ($n = 16$). At 24-h post-procedure, the PVP group displayed significant improvement in VAS (4.7 vs 7.1), although this effect was not sustained by 2 weeks post-procedure [15]. However, the lack of blinding in this trial led to concerns regarding a possible placebo effect.

In August 2009, two highly publicized double-blinded RCTs comparing PVP with a sham procedure were published in the *New England Journal of Medicine* (NEJM) [6, 9]. The findings of both trials contrasted with prior observational data and called into question the usefulness of PVP. The INVEST trial by Kallmes and colleagues randomized 131 patients to receive PVP or a sham procedure (injection of an anesthetic drug against the vertebra), with inclusion criteria including age < 50 years, pain measuring ≥ 3/10 on numerical rating scale (NRS) and fracture age < 1-year duration. By 1-month follow-up, no difference was displayed between groups in either back pain or disability. The second 2009 trial, conducted in Australia by Buchbinder and colleagues with 78 patients, utilized similar inclusion criteria but required no pain severity threshold. Like INVEST, it demonstrated no significant improvement in pain, disability, or quality of life measures after PVP. However, several authors expressed dissatisfaction with the findings of these trials in published responses. In particular, Aebi [16] was concerned about misleading inclusion criteria in the Buchbinder study, including the lack of pain score threshold, as well as the use of small volumes of PMMA cement, and a brief follow-up period. In response to such concerns, Kallmes et al. published a 2013 study that followed up the INVEST cohort over a longer period of 12 months to evaluate longer-term effects [17]. These results demonstrated a modest pain reduction at 1 year with PVP compared with a control procedure, although no differences in functional disability were found. Other concerns related to the "sham" procedure, as the anesthetic drug utilized may have acted as an "active control," contributing to pain relief and thus acting as a confounder in the trials [18, 19].

The VERTOS II trial, published in 2010 in *the Lancet*, was a prospective open-label RCT comparing PVP to medical management for osteoporotic VCFs [20]. Addressing some previous concerns from the 2009 trials, it included fractures of < 6-week duration, with pain severity of ≥ 5/10, focal tenderness on examination, and bone marrow edema on MRI. In total, 202 patients were enrolled to receive PVP ($n = 101$) or medical management ($n = 101$). The PVP group displayed significant pain reduction, which was present both at 1 month (the primary endpoint) and at 1 year. PVP also led to lower medical costs,

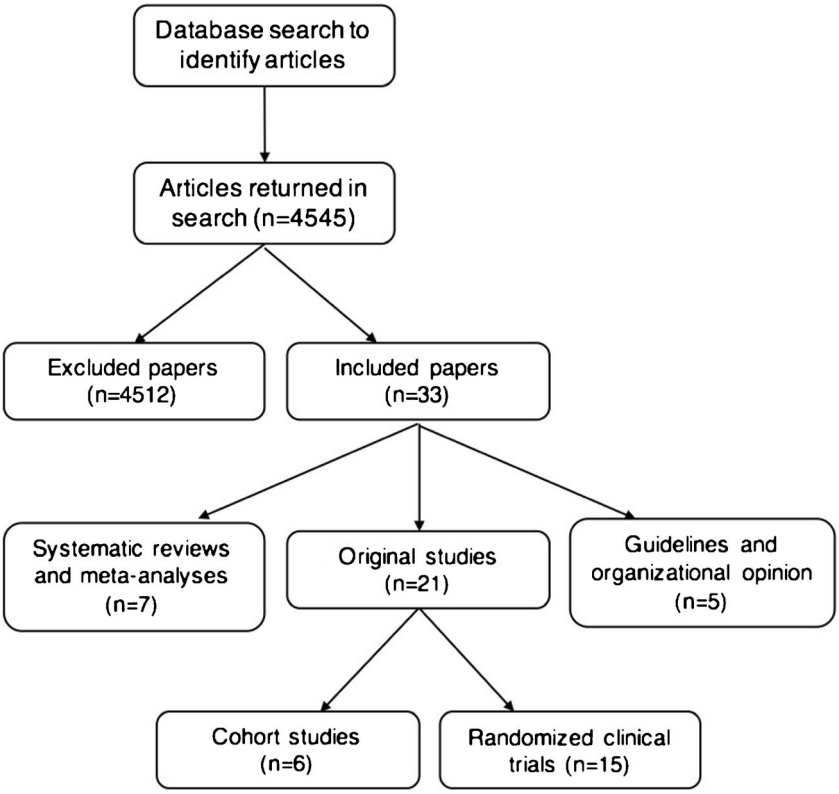

Fig. 1 A flowchart of the search strategy

due to less medication requirements and utilization of ancillary health services. Another important point was the reduction of secondary VCFs in patients treated with PVP, which clarified single-arm observational data from prior studies [20, 21]. However, the key limitation of this trial was a lack of blinding, raising questions of a possible placebo effect. The VERTOS IV trial, another prospective multicenter trial, was designed by the same authors [22]. It aimed to recruit 180 patients with acute back pain of ≤ 6 weeks, to compare treatment outcomes from PVP compared with a sham intervention. At the time of this review, results have not yet been published [22].

Further data from prospective trials, retrospective studies, and systematic reviews has been followed [12, 23–25]. In 2011, another RCT comparing PVP to medical management was published by Farrokhi et al. [26]. In the PVP group, there were statistically significant improvements in pain relief and quality of life sustained for 2 years, as well as improvements in vertebral height and corrections in spine deformity throughout the extended follow-up period of 3 years. Fewer adjacent-level fractures were reported following vertebroplasty [26]. A large multicenter prospective cohort study was published in 2012, including 4547 patients from six Italian centers with painful VCFs of multiple pathologies. Results demonstrated that PVP was effective and safe in the treatment of vertebral fractures, although best outcomes from PVP were obtained in patients with VCFs due to myeloma or trauma [27]. In a 2013 RCT, Blasco et al. compared PVP to conservative management in 125 patients with a 12-month follow-up period [28]. PVP was associated with significant improvements in VAS scores at all time points, as well as greater and earlier improvements in quality of life measures [28].

Standing in contrast to these findings was a systematic review by Buchbinder et al. on the role of PVP in osteoporotic VCFs [29]. They concluded that percutaneous vertebral augmentation procedures should not be considered a valid treatment for vertebral fractures due to insufficient evidence that they reduce pain, function, or disability. In fact, sensitivity analyses performed in this review found that open trials comparing PVP with usual medical care would have overestimated any benefit of percutaneous procedures [29].

In 2016, Yang et al. explored whether PVP could offer extra benefits to aged patients with acute osteoporotic VCFs [30]. A total of 135 patients aged at 70 years or above with acute osteoporotic vertebral compression fractures were randomized to receive PVP or conservative therapy. Early PVP resulted in faster and greater pain relief, improved quality of life, and improved functional outcomes, at every time point: 1 week, 1 month, 3 months, 6 months, and 1 year (all $p <$ 0.0001). Patient surveys carried out at final follow-up indicated that patients in the PVP group had significantly greater overall satisfaction with their given treatment [30].

The 2016 VAPOR study, the most recent RCT on vertebral augmentation, was a large prospective, multicenter, double-blinded trial [31]. Unlike earlier trials, a higher pain score threshold was utilized in inclusion criteria (≥ 7 compared with ≥ 3 in INVEST, and no pain threshold in Buchbinder et al. [6,

9]). All fractures were < 6 weeks in duration. A total of 120 patients underwent PVP ($n = 61$) or a sham procedure involving subcutaneous injection of local anesthetic ($n = 59$). There was significant pain reduction in the PVP group, with NRS pain scores reducing to < 4/10 in 44% of PVP patients ($p = 0.01$); this treatment advantage was durable to 6 months. PVP was also more effective than placebo in reducing disability and resulted in increased height of fractured vertebral body when performed in the acute phase [31].

PKP emerged as an alternative to PVP in 2001. Early uptake of the procedure was supported by pooled observational data from 1710 patients, which demonstrated a significant reduction in VAS pain scores [32]. The 2009 Fracture Reduction Evaluation (FREE) trial is currently the only large multicenter prospective RCT comparing kyphoplasty to medical management for VCFs [33]. It found significantly improved pain scores and quality of life in the PKP group, with effects stable to 6 months [33]. This treatment effect was durable over a 24-month follow-up period. It demonstrated that PKP was associated with greater improvements in pain and disability scores when averaged across the 2-year period [34].

The KAVIAR trial, published in 2014, directly compared PKP and PVP in the management of osteoporotic VCFs [35]. Patients with one to three acute osteoporotic VCFs were randomized to receive PKP ($n = 191$) or PVP ($n = 190$), and were not blinded to their treatment group. Although the trial was terminated with only a third of the enrolment target ($n = 1234$), similar back pain and functional improvements were observed across both groups. Operative time was shorter in the PVP group; there was no statistically significant difference between groups in subsequent VCF fracture risk at 12 or 24 months [35]. A 2015 meta-analysis found that PVP and PKP were similar with regard to long-term pain relief, short- and long-term functional outcomes, and new adjacent VCFs. PKP was superior to PVP in short-term pain relief, and in the improvement of kyphotic angle. It resulted in lower cement leakage and required lower volumes of injected cement. However, PKP had a longer operative time and higher material costs than PVP [36]. Marcia et al. concluded in a 2016 review that both PVP and PKP are effective for pain relief and functional improvement in osteoporotic VCFs, and that current data is insufficient to suggest that clinical outcomes differ greatly between the two [37].

Safety

Overall complication rates are low for both PVP and PKP, occurring in less than 1% of cases [38–40]. The most common complications that have been described in literature are cement leakage, infection, and anesthetic drug reactions [25, 27]. More serious complications are rare but include neurologic deficits resulting from nerve injury, fractures of the rib, sternum or pedicle, pulmonary embolus, hemothorax, pneumothorax, or cement embolism [39, 40].

Asymptomatic leakage of cement outside the vertebral body is common on CT scanning (34% in the VAPOUR trial, 72% in VERTOS II) [20, 31]. Symptomatic cement leakage and embolization of cement are rare [25]. Potential routes for leakage include the epidural space and neural foramina, disc space, paravertebral tissue, and perivertebral venous plexus. Rates of cement leakage are lower in PKP, due to the creation of a low-pressure cavity into which the cement is injected, but overall rates of complications are similar across both procedures [35, 36, 41, 42].

The risk of fracture in the adjacent vertebral body after vertebral augmentation remains controversial. Earlier studies found correlations between vertebral augmentation and collapse of adjacent vertebra. However, more recent evidence has suggested that vertebral augmentation does not increase the risk of new VCFs and may even confer a protective effect [22, 25]. In a 2017 meta-analysis, Zhang et al. compared the incidence of new vertebral fractures after vertebral augmentation or conservative VCF treatment. No significant difference was seen between the two intervention methods in total new vertebral fractures or new fractures adjacent to the treated level. Risk factors for new VCF included lumbar bone mineral density and total number of pre-existing VCFs [43].

Guidelines and medical organization opinion

Vertebral augmentation is supported by the American College of Radiology, American Society of Neuroradiology, American Association of Neurological Surgeons, Congress of Neurological Surgeons, Canadian Interventional Radiology Association, American Society of Spine Radiology, the American Academy of Family Physicians, and the Society of NeuroInterventional Surgery, as a valid pain relief option for VCFs [23, 44, 45]. Most recently, the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) published guidelines in 2017 following the publication of the VAPOUR trial. They acknowledged that evidence for PVP has been conflicting, but that recent data including VAPOUR shows treatment benefit in patients with acute osteoporotic VCFs [25].

Discussion

Positive early observational and retrospective data lead to strong uptake of minimally invasive percutaneous vertebral augmentation procedures as a treatment for osteoporotic VCFs. Uncertainty surrounding their effectiveness emerged following the negative results of the Buchbinder and INVEST trials [6, 9]. However, several limitations to these studies mean that their results appear to deviate from clinical practice. The sham procedures utilized in both trials required the injection of

anesthetic drugs against the vertebral body, potentially resulting in modified pain perception and thus confounding results. Crossover between study groups was allowed after only a brief period, generating potential bias in the evaluation of outcomes [6, 9, 17]. The inclusion criteria utilized by INVEST and Buchbinder were not sufficiently strict, with both trials including fractures of up to 12 months in age, thus allowing for a mixture of acute, subacute, and chronic fractures. Moreover, it is important to underline that Buchbinder and colleagues [6] treated non-confirmed by MR or bone scan of concordance and chronic healed fractures and they did not require neither a physical examination for inclusion in the study nor a minimum pain score threshold that would ensure that only moderate-to-severe fractures were included. INVEST did not require MRI imaging of fractures for inclusion, enrolling patients after only plain radiography. For these reasons, applicability of these study results in clinical practice is limited.

Over the course of these earlier trials, there remained doubt as to the potential influence of the placebo effect, and the effect of including patients with a mixture of acute and chronic fractures causing both moderate and severe pain. Subsequent studies addressed these concerns. The VERTOS II study included only acute fractures and utilized the real-world comparator of conservative management instead of a sham. It demonstrated superiority of PVP over medical management in pain relief and quality of life measures. However, a key limitation inherent in this trial, given the use of conservative therapy as a control, was a lack of blinding, which may have led to an overestimation of treatment effect. In contrast, the VAPOUR trial utilized a placebo procedure designed to improve the blinding of participants while not acting as an active sham; local anesthetic was injected into the subcutaneous tissues but did not numb the periosteum. Moreover, inclusion criteria in VAPOR were stricter than earlier RCTs, requiring patients aged ≥ 60 years, fractures ≤ 6 weeks, pain rated NRS ≥ 7, and bone marrow edema detected on MRI or SPECT CT. In addition, as highlighted in a recently published editorial in *Lancet* by Hirsch and Chandra, medical management can be associated with risk of neurological complications [46]. In both VAPOUR and the RCT by Yang et al., only medically managed patients developed spinal cord compression from further collapse and retropulsion of their VCFs.

Overall, the evidence is consistent with regard to the safety and effectiveness of PVP and PKP, with low rates of serious complications [37, 38]. Moreover, recent evidence also demonstrates that medical management is not without risk.

Conclusions

Vertebral augmentation is a safe procedure, with low rates of serious complications and no increase in subsequent post-treatment fracture risk.

Key points

1. Vertebral compression fractures due to osteoporosis are a common source of increased morbidity and mortality.
2. Vertebroplasty and kyphoplasty are image-guided, minimally invasive procedures that involve the injection of cement into the fractured vertebral body.
3. The key goals of these procedures are pain relief, improved functional status, and enhanced quality of life.
4. Although two high-profile trials in the *New England Journal of Medicine* found no benefit to vertebroplasty, there is recent high-quality randomized controlled trial data supporting the use of vertebral augmentation to treat patients with severe pain within 6 weeks of vertebral compression fracture. There is moderate-quality evidence supporting augmentation for unhealed subacute and chronic osteoporotic fractures.
5. Complications from vertebral augmentation are rare, with low rates of serious complications and no increase in subsequent post-treatment fracture risk.

Compliance with ethical standards

Funding No funding was received for this study.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent Statement of informed consent was not applicable since the manuscript does not contain any patient data.

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