Title Page

Vertebroplasty for acute painful osteoporotic vertebral compression fractures: an update

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Abstract

Vertebral compression fractures (VCFs) are a common cause of back pain and disability and are usually osteoporotic in nature. Therapy aims to adequately control pain and allow early mobilisation and return of function while preventing additional fractures. A proportion of patients do not achieve adequate pain relief using conservative measures alone. Unwanted adverse effects from medications may also ensue. Vertebroplasty represents an alternative treatment option for VCFs. Patients with acute VCFs (≤6 weeks old) may gain the most benefit from vertebroplasty as healed fractures are not as amenable to cement injection. High-quality studies have reported conflicting results regarding the use of vertebroplasty in the treatment of acute VCFs. Despite high quality evidence, varying study designs and heterogenous patient cohorts make interpretation of this data difficult. Only one sham-controlled randomised controlled trial (RCT) has evaluated vertebroplasty exclusively in patients with acute VCFs, reporting favourable results. Pooled data from RCTs also suggests vertebroplasty to be safe. This article provides a concise and critical review of the current literature regarding vertebroplasty for the treatment of acute VCFs.

INTRODUCTION

Vertebral compression fractures (VCFs) are the most common osteoporotic fracture, with a similar mortality to hip fractures.[1] Although many patients with VCFs do not seek medical attention, those who do often present with pain. In 20% of these cases, inpatient hospitalisation is required due to symptom severity.[2] Sufficient analgesia to allow mobilisation and return of function is the primary aim of VCF therapy. Conservative management includes pharmaceuticals, bracing, physiotherapy and long term modification of osteoporotic risk factors.[3] It has been shown that conservative therapy is inadequate in many patients with VCFs and analgesia may precipitate unwanted side-effects.[4,5] Bracing may also be poorly tolerated and has been shown to lead to adverse health outcomes.[6]

There has been an increasing interest surrounding the role of vertebroplasty for the treatment of VCF-related back pain. Vertebroplasty involves image-guided injection of polymethylmethacrylate (PMMA) into the fractured vertebra. This procedure is hypothesised to provide mechanical stability and prevent further collapse and deformity. The proposed mechanism of its analgesic effect is the prevention of micromotion through fracture fixation.[7]

Controversy surrounds the clinical utility of vertebroplasty. While it is well established that vertebroplasty is unlikely to provide benefit for older VCFs, its use for acute VCFs is unclear (VCF age ≤6 weeks). For the purpose of this review, we will use the term 'acute' to refer to VCFs ≤6 weeks old. Four published sham-controlled trials have included differing proportions of patients with acute VCFs, with only one of these exclusively enrolling patients with VCFs ≤6 weeks old. This up-to-date comprehensive review summarises the current literature regarding the use of vertebroplasty for acute VCFs.

OPEN-LABEL RANDOMISED CONTROLLED TRIALS

Three open-label RCTs have evaluated the safety and efficacy of vertebroplasty in acute VCFs (table 1). Rousing et al. were the first to compare vertebroplasty to conservative management in a randomised setting (n=50).[8,9] Most patients had osteoporotic fractures <2 weeks old (n=40) with the remaining fracture ages between 2-8 weeks. Median fracture ages in the vertebroplasty group was 8.4 days and 6.7 days in the conservative arm. Acute fractures were diagnosed on plain film radiographs if a single fracture could be identified. If multiple fractures were visible, magnetic resonance imaging (MRI) was used to differentiate acute from chronic fractures. Volume of PMMA used was not reported. The vertebroplasty group reporting significant improvement in Visual Analogue Scale (VAS) pain scores at 24 hours and 1 month compared to conservative management, suggesting that vertebroplasty may be an appropriate treatment for patients with severe acute/subacute fracture pain. The vertebroplasty group also required shorter hospital stay to achieve pain control, however this group also had less significant pain at baseline. No significant difference in these scores were seen at 3 or 12 months, although this trial was not powered for the 3 month endpoint. Weaknesses of this study include its small single-centre nature and the missing baseline VAS scores for 27% of patients. The delay between enrolment and performance of vertebroplasty was also not stated.

VERTOS II was the first RCT to exclude patients with VCFs >6 weeks old (n=202) and was the first study to support the use of vertebroplasty in acute/subacute VCFs.[10] Median duration of back pain in the vertebroplasty group was 29.3 days and vertebroplasty was performed at a mean of 5.6 weeks after pain onset. VERTOS II reported a statistically significant improvement in VAS scores at all time points (1 day, 1 week, 1, 3, 6 and 12 months) with vertebroplasty compared to conservative management. Patients required significantly less analgesia after 1 day and 1 month following vertebroplasty, however this benefit did not persist. A significant improvement in disability and QoL was also reported in the vertebroplasty group, with patients gaining an average of 120.3 pain free days (VAS ≤3). Criticisms of this study included the lack of a sham procedure and the potential for these findings to be placebo-related. Post-hoc analysis also showed 60% of patients achieved adequate pain control within 12 months.[4]

Only one RCT has evaluated the safety and efficacy of vertebroplasty in patients with VCFs ≤3 weeks old (n=135).[11] Mean duration of back pain in the vertebroplasty group was 5.5 days and vertebroplasty was performed at a mean of 8.4 days after injury. At all time points over a 1 year period, vertebroplasty provided significantly more pain relief than conservative management as measured by VAS scores. Perceived benefits were significantly greater at 1 year following vertebroplasty. Disability and QOL scores also significantly improved at all time points during follow up. In addition to being non-blinded and having no placebo group, one major limitation was that conservatively treated patients were required to lie in bed for 2 weeks following diagnosis. This is not usual practice given the well-established sequelae of immobility.[12] Participants in the vertebroplasty group also did not receive supplementary analgesia.

BLINDED RANDOMISED CONTROLLED TRIALS

Four blinded RCTs have assessed vertebroplasty in patients with acute VCFs. Two of these were published concurrently in 2009 and reported unfavourable results with vertebroplasty. Buchbinder et al. reported no significant difference in pain reduction, quality of life scores, physical functioning or perceived improvement at any time point over a 6-month period with vertebroplasty compared to the sham group (n=78).[13] Median duration of back pain in the vertebroplasty group was 9 weeks (IQR 3.8-13) and the proportion of patients with VCFs <6 weeks was low in both groups (32% in each). Patients with back pain up to 12 months were recruited. Physical examination was not required. Despite having a target enrolment of 200

patients, slow recruitment led to only 78 participants after 64% of eligible participants declined involvement. Additionally, two of the four enlisted hospitals withdrew meaning that 68% of the procedures were performed in one hospital by one radiologist, raising the possibility of selection bias. Blinded RCT power analysis is usually based on detecting a 15% difference in mean pain outcomes requiring 120 patients and thus this study was underpowered.

The Investigational Vertebroplasty Efficacy and Safety Trial (INVEST) also reported unfavourable results with vertebroplasty compared to sham (n=131).[14] Both groups reported a similar improvement in pain and disability after 3 days. No significant difference in pain, disability or quality of life was seen between groups after 1 month either, however there was a trend towards a significantly higher rate of clinically meaningful improvement in pain (>30% from baseline) with vertebroplasty (64% vs 48%, p=0.06). Mean duration of back pain was 16 weeks (IQR 10-36) and patients were required to undertake 4 weeks of medical therapy prior to enrolment, essentially excluding all patients with acute fractures. Forty percent of participants had fractures <3 months while 36% had fractures >6 months. The proportion of patients with back pain of ≤6 weeks is not stated. Again, patients with back pain up to 12 months were recruited. MRI or radio-isotope bone scan was only performed if the fracture age was uncertain meaning that radiographically occult fractures may have been missed and patients with non-VCF-related pain may have been included. Seventy percent of patients eligible for inclusion declined, again raising concerns about patient selection. Investigators also suggested that patients in the control group likely had undetected unsatisfactory pain outcomes as the 3-month crossover rate in the control group was high (51%).

VAPOUR was the first double-blinded sham-controlled RCT to evaluate vertebroplasty in patients exclusive with VCFs ≤6 weeks old.[5] It is the only blinded trial powered to detect a 15% difference in patients with a VCF age of ≤6 weeks. VAPOUR's clinical primary endpoint was a conversion from severe to mild pain at 2 weeks, with severe pain defined as an NRS ≥7/10 at baseline (enrolment criterion) and mild pain defined as an NRS <4/10. This is the only blinded trial to define a clinically significant benefit measured in individual patients rather than compare mean group pain scores. Significantly more patients had an NRS pain score <4 at 10-14 days following vertebroplasty compared to sham (44% vs 21%;

p=0.01). This advantage persisted at all time points to 6 months, with the biggest difference between groups seen at 4 weeks. Mean reduction in NRS pain was also significantly greater with vertebroplasty at all time points up to 6 months. Additionally, vertebroplasty resulted in significantly less analgesic use at 3 months and 6 months, a significantly improved general QoL at 1 and 6 months and a significantly improved disease-specific QOL at 14 days and 6 months. These led to a median reduction of 5.5 hospital inpatient days in the vertebroplasty group which, in a double-blinded study, must be due to improvement in pain and function. Interestingly, 77% of patients had VCFs ≤3 weeks old. There was a trend towards significance in the subgroup analysis between patients with VCFs ≤3 and >3 weeks, although there were insufficient patient numbers in the VCF >3 week group to achieve statistical significance. VAPOUR assessed 302 patients for suitability and 22% (n=34) refused to participate, considerably less than that of Buchbinder et al. and INVEST. The major limitation of VAPOUR was the bias towards a single centre, with 85% of procedures were performed at one institution.

VERTOS IV is the most recent double-blinded sham-controlled RCT to evaluate the safety and efficacy of vertebroplasty in VCFs (n=180).[15] Patients were recruited via written questionnaires from referrals for spinal radiographs rather than referrals for vertebroplasty. Median duration of back pain prior to vertebroplasty was 6.1 weeks (IQR 4.1-8.7). Mean VAS scores did not differ between groups at multiple time points between 1 day and 1 year postprocedure despite both groups showing improvement. Analgesia use, QoL and disability during 12-month follow up were also similar between groups. Despite the published protocol listing inclusion criteria of VCF ≤6 weeks, a number of patients with VCFs ≤9 weeks were included due to slow recruitment (24% of vertebroplasty group, 14% of sham group). However, this is still misleading as fracture age was calculated at the time of radiography and there was a 13-day delay (IQR 7-18 days) between this and intervention. As a result, approximately 50% of patients had fractures over 6 weeks old at the time of vertebroplasty and some are likely to be closer to 12 weeks of age.

META-ANALYSES

The first two published placebo-controlled RCTs were combined in a 2011 meta-analysis by Staples et al.[16] By publishing concurrently and meta-analysing, the power issue of these papers individually was improved however their inherent limitations remained. Unsurprisingly, this analysis reported no significant difference between placebo and

vertebroplasty groups with respect to pain, disability or health status at any time point up to 1 month. Subgroup analysis again reported no difference between groups based on pain >6 weeks, severe pain at baseline or mild/moderate pain at either the two weeks/one week or one month time points. Staples et al. also reported no difference between groups with pain ≤6 weeks, however this study was underpowered for this analysis (25 vertebroplasty patients, power for 15% difference required 60 patients). A 2012 meta-analysis of 9 published prospective trials found that the efficacy of vertebroplasty on pain relief for patients with acute VCFs was greater than that of non-operative therapy at 1 to 29 days and at 90 days.[17] Several other meta-analysis have supported the use of vertebroplasty, however these have not reported on outcomes relating specifically to acute VCFs.[18–21]

The first Cochrane review for vertebroplasty was published in 2015.[22] This also detailed the review protocol which has not been updated and still applies to the more recent Cochrane review published in 2018. This included 21 trials and declared that high- to moderate-quality evidence suggested vertebroplasty provides no clinically important benefits with respect to pain, disability, QoL or treatment success after 1 month.[23] No mention was made of these outcomes after this time point. Subgroup analysis also suggested that VCF age did not impact the efficacy of vertebroplasty (≤6 weeks vs >6 weeks). VERTOS IV was the dominant weight in this analysis and the entire vertebroplasty group from this trial was included in the subgroup analysis for VCFs ≤6 weeks despite approximately half these patients having VCFs >6 weeks old. This review also lists VERTOS IV as fracture duration <9 weeks which is false. Consequently, approximately one quarter of this subgroup actually had VCFs >6 weeks old and thus this conclusion is misleading. The safety of vertebroplasty was again deemed to be unclear. A revised Cochrane review released in June declared that vertebroplasty provided 'little clinical benefit' in treating VCFs despite including the same trials as the original review after receiving complaints about the original report (discussed below).[24]

CONTROVERSY

The quality of evidence assessing the clinical utility of vertebroplasty is variable. The interpretation of these results is challenging due to the disparate clinical variables of each blinded trial and the difficultly associated with comparing open-label and blinded RCTs. These are summarised in table 2. VAPOUR is the only double-blinded sham-controlled RCT to support the use of vertebroplasty in acute VCFs. It also possesses a unique patient cohort.

Participants were older and had more severe pain compared to other trials, with a substantially higher pain score (NRS ≥7) required for inclusion. It is the only blinded trial to list osteoporosis as inclusion criteria and the majority of participants were inpatients. Fracture age at enrolment was also considerably less as this study is the only blinded RCT to truly exclude patients with VCFs >6 weeks old.

VAPOUR used more PMMA cement compared to other RCTs, likely reflecting how the volume of PMMA accepted by bone without undue resistance is higher in fresher fractures. The principle of the VAPOUR trial was to support the bone top to bottom and side to side which requires larger PMMA volumes, particularly in more acute fractures ("vertebral fill technique").[5] Attempting to inject this volume into older fractures is not possible and not recommended and it is the distribution of cement, not the volume, which is the technical end-point. The smaller volumes in the 2009 trials reflects the chronicity of fractures, which resist PMMA injection after healing.

Vertebroplasty Cochrane reviews have relied exclusively on the meta-analysis of blinded trials to draw its conclusions. Meta-analyses possess the benefit of statistically analysing larger patient populations over multiple sites. This is particularly useful when individual studies are underpowered as seen with Buchbinder et al. and INVEST. However, analysed studies should possess similar patient populations receiving similar treatments. When patient groups are heterogenous the conclusion is less robust. These Cochrane reviews have combined VAPOUR with clinically different trials, despite protocol specifying that heterogeneous trials would be analysed individually.[25] Differences in baseline pain, hospitalisation status, timing of intervention, presence and severity of osteoporosis and vertebroplasty technique are crucial differences between included trials. Additionally, when combining heterogenous studies, the dominant weighting from one trial, as seen with VERTOS IV, is compounded further. For studies with conflicting results and heterogenous cohorts, it is often more appropriate to analyse studies individually. This also allows for more targeted patient selection in clinical practice. Despite a letter of complaint to Cochrane addressing these issues and more, they remained in the November 2018 update.[26]

SAFETY

Safety outcomes can be summated from both blinded and open-label RCTs. These confirm

that the risks are small. Nevertheless, a number of clinically important adverse events may occur with vertebroplasty. These include spinal cord compression, neurological deficits, cement embolism and osteomyelitis.[27] Recent Society of Interventional Radiology (SIR) guidelines report major complications as <1%.[28] The most common complication with vertebroplasty is cement extravasation. The reported incidence of local extravasation is 41.2% (with 98% considered minor) and distant cement embolus is 0.1%.[29] Cement embolism is usually asymptomatic but rates as high as 26% have been reported.[30] In addition to cement extravasation rarely being problematic, it may be so that the incidence of PMMA extravasation reduces with more acute fractures and the use of newer, high viscosity PMMA.

Whilst it is thought that an increased cement volume aims to stabilise an acutely collapsed fracture, this is at the expense of a greater risk for cement extravasation.[31] Despite using a larger volume of cement, VAPOUR's serious complication rate was still below standard stipulated in SIR guidelines. However, care should be taken when injecting large volumes of cement as the optimal volume is still an ongoing area of research.[32–34]

Patients who undergo conservative therapy may also be at harm from further collapse, deformity and neurological compromise. Two patients each in VAPOUR's control group and Yang et al.'s conservatively managed arm required surgical decompression after suffering interval vertebral collapse and retropulsion with resultant spinal cord compression. One of these patients suffered significant permanent neurological sequelae. In addition, some suggest that vertebroplasty leads to an increased risk of adjacent vertebral fractures due to the biomechanical effects of cement stiffness.[35,36] Meta-analyses have not found an increased risk of adjacent vertebral fractures after vertebroplasty.[37–39]

CONCLUSION

Vertebroplasty represents a contentious management option for people with acute VCFs. Much of the literature surrounding vertebroplasty for VCFs ≤6 weeks is limited by varying study designs, small sample sizes and heterogenous cohorts. All RCTs evaluating vertebroplasty exclusively in patients with acute VCFs found it to be superior to conservative treatment or placebo, including a high-quality sham-controlled RCT. Despite recent Cochrane reviews, it may be that vertebroplasty has clinical value in treating acute VCFs, particularly in patients with severe pain.

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Trial	Rousing (2009 and 2010)	VERTOS II (2010)	Yang (2016)
Minimum age (years)	>65	≥50	≥70
Fracture age	≤8 weeks	≤6 weeks	≤3 weeks
Minimum pain	Severe enough to impair independence	VAS score ≥5	VAS score ≥5
T-score	Nil	T-score ≤-1.0	T-score ≤-1.0
MRI/SPECT	N	Y	Y
Control arm	Medical treatment, physiotherapy, bracing	Medical treatment	Bed rest for ≥ 2 weeks, medical treatment, physiotherapy, bracing
Number of patients	50 (V: 26, C: 24)	202 (V: 101, C: 101)	107 (V: 56, C: 51)
Mean/median fracture age	V: 8.4 days, C 6.7 days	V: 29.3 days, C: 26.8 days	V: 5.5 days, C: 5.6
Mean/median fracture age at performance of vertebroplasty	Not mentioned	5.6 weeks	8.4 days
Mean T-score	Not mentioned	V: -3.0, C: -3.0	V: -3.3, C: -3.2
Preprocedural imaging	X-ray +/- MRI/SPECT CT (if >1 fracture on x-ray)	X-ray, MRI	X-ray, MRI
Mean cement volume	Not mentioned	4.1ml	4.5ml
Inpatients included (Y/N; %)	Y; not mentioned	N; 0%	Not mentioned
Mean initial pain score	VAS scale	VAS scale	VAS scale

	V; 7.5, C: 8.8	V: 7.8, C: 7.5	V: 7.5, C: 7.7
Results	Significant improvement in VAS scores with vertebroplasty at 24 hours and 1 month, no significant difference between groups at 6 or 12 months	Significant improvement in VAS scores at all time points with vertebroplasty (1 day, 1 week, 1, 3, 6 and 12 months)	Significant improvement in VAS scores at all time points with vertebroplasty (1 day, 1 week, 1, 3, 6 and 12 months)
Vertebroplasty-related complications	Nil	2 pain-related vasovagal episodes, 1 asymptomatic pulmonary cement embolus	Nil
Conservative therapy-related complications	Nil	Nil	2 patients experienced vertebral collapse and spinal cord compression requiring surgical decompression

Table 1. Non-blinded RCTs evaluating vertebroplasty in patients with acute VCFs.

Trial	Buchbinder et al	INVEST	VAPOUR	VERTOS IV
Minimum age (years)	None	50	60	50
Minimum pain score	None	NRS pain ≥3	NRS pain score ≥7	VAS pain score ≥5
Fracture age	≤12 months	≤12 months	≤6 weeks	≤12 weeks
Mean Age	V: 74.2, C: 78.9	V: 73.4, C: 74.3	V: 80, C: 81	V: 74.7, C: 76.9
Preprocedure MRI/SPECT CT	Y	Only if fracture age uncertain	Y	Y
Inpatients included (Y/N; %)	Y; not mentioned	Excluded	Y; V: 34 (56%), C: 34 (58%)	Not mentioned
T scores	Lumbar T score <2.5: V: 21, C: 21	Not mentioned	Mean lumbar T score: V: -4.1, C: -4.5	Mean lumbar T score: V: -2.4, C: -2.4
Mean fracture age	All patients: 11.7 weeks V: 9 weeks, C: 9.5 weeks (median)	V: 16 weeks, C: 20 weeks All patients: 22.5 weeks	V: 2.8 weeks, C: 2.4 weeks	V: 43 days, C: 36 days
Proportion with fracture age ≤6 weeks	32%	Not mentioned	All	Unclear

Mean initial pain score	NRS scale V: 7.4, C: 7.1	NRS scale V: 6.9, C: 7.2	NRS scale V: 8.6, C: 8.6	VAS scale V: 7.7, C: 7.9
Mean cement volume	2.8ml	Not reported	7.5ml	5.1ml

Table 2. Key clinical differences between sham-controlled RCTs evaluating vertebroplasty in patients with acute VCFs.