

VERTEBROPLASTY AS A TREATMENT FOR OSTEOPOROTIC COMPRESSION FRACTURES *A Technology Assessment*

INTRODUCTION

The California Technology Assessment Forum (CTAF) is requested to review the scientific evidence for the use of vertebroplasty for the treatment of osteoporotic vertebral compression fractures. This review was prompted by the publication of two randomized controlled trials (RCT's) of vertebroplasty.

BACKGROUND

Vertebral compression fractures are a significant morbidity and mortality related outcome of both primary and secondary osteoporosis.¹⁻³ Approximately 10 million Americans older than 50 have osteoporosis, with 34 million more at risk, resulting in 1.5 million fragility fractures (spine, hip, forearm) annually.¹ Remaining lifetime risk for diagnosed vertebral fracture is estimated to be 16% for white women over age 50. While osteoporosis is more common among women, and more common among whites, it can and does occur in men and in any race/ethnic group. Most osteoporotic fractures heal within a few weeks or month, but a minority of patients has persistent pain that does not respond to conservative measures. In addition, vertebral fractures due to osteoporosis are associated with a decline in function and mortality, particularly for elderly patients.^{2, 3}

Traditional treatment for patients with osteoporotic vertebral compression fractures is medical management and includes bed rest, analgesics, and bracing. In the 1980's, a percutaneous interventional technique called vertebroplasty, which involves augmentation of vertebral compression fractures with polymethylmethacrylate (PMMA), was developed to treat persistent pain from compression fractures. Vertebroplasty was first used in the United States in the early 1990's and has since become fairly widely used based on observational data only. This review was prompted by the publication of the first two RCT's of vertebroplasty compared to sham treatments.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

Vertebroplasty as a procedure and as such does not require FDA clearance. However, there are several manufacturers of PMMA which have received FDA clearance through the 510(k) process.

In addition, there are several manufacturers of delivery systems for PMMA who have received clearance for their devices.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline, Embase, and Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched for relevant references through December 2009. We included studies if they were 1) English-language published articles, 2) assessed the effect of vertebroplasty on patients with vertebral fractures due to osteoporosis, 3) reported on clinical outcomes of pain, functional status or quality of life, 4) reported pre- and post-procedure values for outcomes, and 5) had a sample size of ≥ 100 patients for non-comparative observational studies. The Technology Evaluation Center published a similar review in September 2008,⁴ and found six observational case series,⁵⁻¹⁰ and two studies comparing vertebroplasty to conservative treatment^{11, 12} which met these inclusion criteria. Our updated search from 2008 through December 2009 and review of relevant references and bibliographies found an additional five observational case series (two by the same authors),¹³⁻¹⁷ one additional study comparing vertebroplasty to conservative treatment,¹⁸ and two randomized controlled trials comparing vertebroplasty to sham vertebroplasty.^{19, 20}

Level of Evidence: 1, 3, 5
TA Criterion 2 is met.

TA Criterion 3: The technology must improve net health outcomes.

Observational Case Series

All 11 of the published observational case series reporting on ≥ 100 patients who underwent vertebroplasty for spinal compression fracture found positive results.^{5-10, 13-17} These studies are a mix of prospective and retrospective designs. All of them assess improvement in pain scores, and many also assess mobility, oral analgesic use, and quality of life. They range from 100 to 624 patients, and follow-up ranges from 24 hours to three years; however studies with more than one month follow-up appear to have significant drop-off in participation (when reported). Many studies include patients with etiologies for their compression fractures other than osteoporosis (e.g. cancer, trauma); although even in these studies osteoporosis is the predominant etiology. Studies vary in other inclusion criteria as well, with different requirements for fracture age and prior conservative treatment. One study investigated characteristics associated with better outcomes and found that the presence of signal abnormalities on magnetic resonance imaging (MRI), $<70\%$ vertebral height collapse, and healthier patients at baseline were all associated with better outcomes on visual analogue pain scales.⁵ The non-comparative nature of all of these studies makes it impossible to know if the observed improvements after vertebroplasty would have also occurred over time with optimal conservative management anyway.

Comparison to Conservative Treatment

Three publications did compare vertebroplasty to conservative management. Two were non-randomized studies with small and unequal group sizes,^{11, 12} and one was a small randomized trial.¹⁸ The study by Voormolen et al prospectively investigated pain, oral analgesic use and quality of life for 18 patients with subacute or chronic osteoporotic compression fractures who underwent vertebroplasty compared with 16 similar patients who were given pain management.¹² At one day post-procedure the vertebroplasty group had lower pain scores than the pain management group; however this difference did not persist at two weeks. At two weeks, the vertebroplasty group did have less analgesic use and moderately improved quality of life compared with the pain management group; it is important to note that the primary intervention for the pain management

group was optimization of pain medications, leading to increased analgesic use. This study allowed the pain management group to cross-over to vertebroplasty at two weeks. The Diamond et al study enrolled uneven groups of patients with acute osteoporotic fracture - 55 (vertebroplasty) and 24 (conservative therapy).¹¹ Compared with the conservative therapy group, the vertebroplasty group had significantly reduced pain scores and improved physical functioning at 24-hours post-procedure; however there was no difference between groups on either outcome at six weeks and at 6-12 months: both groups improved. The Rousing et al study randomized 50 patients with either acute (< two week) or subacute (2-8 weeks) fractures to either vertebroplasty or conservative treatment.¹⁸ At three month follow-up both groups experienced significant and equal pain reduction; the vertebroplasty group achieved this pain reduction within the first 24 hours of the procedure. Both the Diamond et al and Rousing et al studies imply that for acute, and possibly subacute, fractures vertebroplasty at best speeds up the improvement that occurs as part of the natural history of this disease for most patients.

Comparison to Sham Vertebroplasty

There are two RCT's comparing vertebroplasty to sham vertebroplasty for the treatment of osteoporotic compression fractures, both of which were published in August 2009.^{19,20} Both trials were double-blinded multi-center trials. Both utilized sham vertebroplasty as controls, but with somewhat different technique. The Buchbinder et al study performed the procedure through introduction of the needle and an anesthetic facet injection was done; whereas in the Kallmes et al study, pressure was applied on the back after a subcutaneous lidocaine injection in lieu of needle introduction and facet injection. In both sham procedures, patients were given conscious sedation and the smell of PMMA pervaded the room. In both studies, the fractures could be up to 12 months old as determined by the presence of back pain for 12 months or less. In the Buchbinder et al study, all patients underwent an MRI prior to inclusion to identify a fracture and/or edema at the level of pain. In the Kallmes et al study, an MRI or bone scan was only done if the age of the fracture was indeterminate. Both studies had difficulty with recruitment. In the Buchbinder et al study, 30% of potentially eligible participants declined participation. In the Kallmes et al study, recruitment goals were significantly reduced after slow recruitment, requiring greater differences

between groups for a statistically significant difference to be detected; however, revised recruitment targets appeared sufficient for detecting clinically significant differences. While both studies were small, neither had much drop-out prior to outcome assessment, and both employed an intention to treat analysis. Neither study found any statistically or clinically significant differences between the vertebroplasty and sham groups in their primary or secondary outcomes, including pain at three months, quality of life, disability, perceived recovery (Buchbinder et al) and pain and disability at one month, quality of life or use of opioid medications (Kallmes et al). Both examined potential interaction of results with duration of symptoms and found no significant interaction.

TA Criterion 3 is not met.

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Table 1. Randomized controlled trials comparing vertebroplasty to sham -vertebroplasty for treatment of painful osteoporotic compression fractures

Study	Design	Sham	Inclusion/Exclusion Criteria	Outcomes	Results	Comments
Buchbinder 2009	<p>Randomized; parallel-group</p> <p>Vertebroplasty N=38 Sham-control N=40</p> <p>Triple blinded (patients, investigators, outcome adjudicators) Interventional radiologists (not blinded) trained and experienced in vertebroplasty performed standardized procedures.</p>	<p>Patients were randomized just prior to the procedure. After skin incision, and placement of 13-gauge needle on the posterior lamina, the central sharp stylet was replaced with a blunt stylet and the vertebra was gently tapped. PMMA was prepared in the room.</p>	<p>Outpatient, inpatient & ED recruitment. Four clinical sites in Australia.</p> <p>INCLUSION: Back pain for ≤ 12 months. 1-2 'recent' vertebral fractures (≥ Genant grade 1; edema / fracture line or both on MRI).</p> <p>EXCLUSION: >2 recent fractures. Spinal cancer. Neurologic complications. Osteoporotic vertebral collapse >90%. Destruction of posterior wall / retropulsed bony fragment / bony fragments impinging on spinal cord. Medical contraindication to emergency decompressive surgery. Previous vertebroplasty. Dementia.</p>	<p>PRIMARY: Change in over-all pain score at 3 months (0-10 scale; 1.5 minimal clinically important difference)</p> <p>SECONDARY: Quality of life scales QUALEFFO – vertebral fracture & osteoporosis specific 0-100 measure. AQoL – sensitive to changes in frail elderly 0-1 measure (higher is better; .06 minimal clinically important difference). EQ-5D – 0-1 measure (higher is better; .074 minimal clinically important difference).</p> <p>Scores for pain at rest and in bed at night (0-10).</p> <p>Modified Roland-Morris Disability Questionnaire (0-23; lower is better; 3 points minimal clinically important difference).</p> <p>Perceived recovery (pain, fatigue, overall health) 7-point ordinal scale – 'moderately' or 'a great deal' better considered successful.</p>	<p>No difference for primary outcome: between group mean difference in pain score at 3 months 0.6 (95% CI -0.7 to 1.8), overall moderate decrease in pain for both groups (vertebroplasty 2.6±2.9 vs. sham 1.9±3.3).</p> <p>No statistically or clinically significant between-group differences in any other outcomes at 1, 3 or 6 months, or over time.</p> <p>No significant interactions of results with duration of symptoms (<6 weeks vs. ≥6 weeks), sex, clinical site, previous vertebral fractures.</p>	<p>30% of potentially eligible participants declined participation.</p> <p>Enrollment slower than anticipated; insufficient power to assess 2 year repeat vertebral fracture outcome.</p> <p><10% dropout at 3 and 6 months.</p> <p>Intention to treat analysis.</p> <p>P-values not adjusted for multiple comparisons.</p>



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Study	Design	Sham	Inclusion/Exclusion Criteria	Outcomes	Results	Comments
Kallmes 2009	<p>Randomized – stratified, block by site.</p> <p>Vertebroplasty N=68 Sham-control N=63</p> <p>Double blinded (patients, all study personnel except study statisticians). Vertebroplasty practitioners all experienced.</p>	<p>Patients were randomized while under conscious sedation and after 1% lidocaine was infused in subcutaneous tissues overlying the pedicle of the target vertebra (e). In the sham procedure, pressure was put on the patient's back and the methacrylate monomer was opened in the room, but the needle was not placed.</p>	<p>11 Clinical sites – 5 in US, 5 in UK, 1 in Australia.</p> <p>INCLUSION: Back pain of ≥ 3 (0-10 scale) despite standard medical therapy. 1-3 vertebral fractures (T4-L5) ≤ 12 months old & if age indeterminate marrow edema on MRI or bone scan.</p> <p>EXCLUSION: Spinal cancer in target vertebral body. Retropulsed bony fragments. Concomitant hip fracture. Active infection. Uncorrectable bleeding diathesis. Surgery within previous 60 days. Dementia. No telephone. Inability to communicate in English.</p>	<p>PRIMARY Modified Roland-Morris Disability Questionnaire (RDQ) score at 1 month (0-23; lower is better; 3 points minimal clinically important difference).</p> <p>Average pain over preceding 24 hours at 1 month (0-10 scale; 1.5 minimal clinically important difference).</p> <p>SECONDARY Pain Frequency Index score Pain Bothersomeness Index score SOF-ADL scale EQ-5D scale Use of opioid medications SF-36 Physical Component and Mental Component Summary subscale scores</p>	<p>No difference for primary outcomes: 1) Between group mean difference in RDQ score at 1 month 0.7 (95% CI -1.3 to 2.8), overall moderate decrease in disability for both groups (vertebroplasty mean 12.0 ± 6.3 vs. sham mean 13.0 ± 6.4). 2) Between group mean difference in pain score at 1 month 0.7 (95% CI -0.3 to 1.7), overall moderate decrease in pain for both groups (vertebroplasty mean 3.9 ± 2.9 vs. sham mean 4.6 ± 3.0).</p> <p>No statistically or clinically significant between-group differences in any other outcomes at 1 month.</p> <p>No significant interaction of results with duration of symptoms (≤ 13 vs. 14-26 vs. 27-52 weeks)</p>	<p>Recruitment difficulty led to change in sample size and statistically detectable difference.</p> <p>Statisticians saw unblinded data.</p> <p>Not all fractures were assessed by MRI/bone scan.</p> <p>Participants allowed to cross-over at 1 month: 1 control and 2 vertebroplasty group crossed over before 1 month.</p> <p><5% dropout at 1 month.</p> <p>Intention to treat analysis.</p> <p>P-values not adjusted for multiple comparisons.</p>

TA Criterion 4: The technology must be as beneficial as any established alternatives.

Because TA criterion 3 was not met, by definition TA criterion 4 cannot be met. The primary established alternative for osteoporotic vertebral compression fractures is conservative medical management. This can include bracing, non-opioid and opioid analgesics, and physical therapy.²¹ As discussed above the few studies which have compared vertebroplasty to conservative medical management indicate that vertebroplasty may achieve pain relief sooner than conservative treatment for acute fractures; however, the difference between the two is erased somewhere between two and six weeks. In addition, vertebroplasty exposes patients to the possibility of procedure related complications such as cement leakage and rarely cement embolism, and, although somewhat controversial, possible increased risk of new onset adjacent-level fractures.²² ²³ An ongoing trial in The Netherlands, VERTOS II, plans to enroll 200 patients with new (<6 weeks) fractures and randomize them to vertebroplasty or conservative treatment; this study may provide more information about whether vertebroplasty can provide early pain relief for patients with acute fractures and at what additional risk.²⁴

Balloon kyphoplasty, a procedure similar to vertebroplasty, but which differs largely in its introduction of an inflatable bone tamp (balloon) into the vertebral body to create a space for injection of the cement, is another alternative therapy.²⁵ While the literature to date comparing vertebroplasty to balloon kyphoplasty has shown mixed results,²⁶⁻³⁶ two published metaanalyses demonstrate that the two procedures appear to be comparable in their benefits.^{37, 38} A RCT of 100 patients comparing vertebroplasty and kyphoplasty also demonstrated no significant difference in pain relief with the two procedures.³⁹ This body reviewed balloon kyphoplasty in June 2009, concluding that balloon kyphoplasty met CTAF criteria for effectiveness and improvement in health outcomes for recent (<3 month old) osteoporotic vertebral compression fractures confirmed by MRI; this conclusion was based in large part on a single randomized trial comparing balloon kyphoplasty to conservative treatment.^{40, 41} There has been no published comparison of balloon kyphoplasty to a sham control. It remains to be seen if a trial of balloon kyphoplasty compared with sham kyphoplasty would demonstrate more benefit than the sham control or than vertebroplasty has compared to a sham control.

TA Criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside of the investigational setting.

Although vertebroplasty has been used broadly outside of investigational settings, because TA criterion 3 and 4 were not met, TA criterion 5 cannot be met.

TA Criterion 5 is (not) met.

CONCLUSION

Vertebroplasty has been in broad clinical use for two decades based largely on case series data. Now this broad use has been called into question by the first two RCT's comparing vertebroplasty to sham controls. Both of these studies have been criticized for small sample size, potential selection bias due to difficulty with recruitment, possible inclusion of more chronic fractures with incomplete use of MRI/bone scan to confirm fractures, and their discordance with years of prior observational studies.⁴² While these two trials are not perfect, they are by far the highest quality studies to date of vertebroplasty. Their difficulty in recruitment demonstrates the importance of conducting good RCTs prior to dissemination of technology into broad clinical use. In addition, these trials' results are not discordant with the prior comparative studies discussed above which also found no difference between vertebroplasty and conservative treatment except in the initial post-procedure period. It is possible that there is a role for vertebroplasty for a select group of patients with disabling pain immediately following an acute fracture and who are willing to risk an adverse event rather than wait out the healing powers of time and conservative treatment. The VERTOS II trial results may assist clinicians and their patients in weighing the risks and benefits of vertebroplasty; however, a larger sham-controlled trial of patients with verified acute fractures would be more useful in this regard. Additionally, in light of the vertebroplasty RCT results, the question of whether balloon kyphoplasty is indeed better than a sham procedure remains an open one.

DRAFT RECOMMENDATION

- It is recommended that vertebroplasty *does not meet* CTAF criteria 3-5 for safety, effectiveness and improvement in health outcomes for the treatment of osteoporotic vertebral compression fractures.

February 17, 2010

This is the first review of this technology by CTAF since 2003.

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RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center conducted an assessment of Percutaneous Vertebroplasty or Kyphoplasty for Vertebral Fractures Caused by Osteoporosis in December 2009. The Medical Advisory Panel (MAP) concluded that TEC criteria were not met for either vertebroplasty or kyphoplasty.

Centers for Medicare and Medicaid Services (CMS)

Neither a National Coverage Determination nor a Local Coverage Determination (CA) was found in a review of the CMS web site. However, documents regarding coding and payment were found.

California Orthopaedic Association (COA)

The COA has been invited to attend the meeting and to provide an opinion regarding the use of this technology.

California Association of Neurological Surgeons (CANS)

CANS has been invited to attend the meeting and to provide an opinion regarding the use of this technology.

Society of Interventional Radiology (SIR)

SIR has provided an opinion regarding this technology. A representative of SIR has been invited to attend the meeting.



North American Spine Society (NASS)

NASS has been invited to provide an opinion regarding this technology. A representative of NASS has been invited to attend the meeting.

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ABBREVIATIONS USED IN THIS REVIEW

CTAF	California Technology Assessment Forum
RCT	Randomized controlled trial
PMMA	Polymethylmethacrylate
DARE	Database of Abstracts of Reviews of Effects
ED	Emergency department
QUALEFFO	Quality of life questionnaire
AQoL	Assessment of quality of life
EQ-5D	Descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression)
CI	Confidence interval
RDQ	Roland-Morris Disability Questionnaire
SOF-ADL	Study of Osteoporotic Fractures and. Activities of Daily Living questionnaire
SF-36	Short form 36
MRI	Magnetic resonance imaging

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