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Editorial

Vertebroplasty for vertebral compression fractures: Placebo or effective?

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Abstract

Vertebral compression fractures (VCFs) are a major cause of pain and disability. Here, we reviewed six randomized control trials (RCTs) focusing on the efficacy vs. placebo effect of vertebroplasty (VP) for symptomatic VCF. Four RCTs involved a nonsurgically treated control group. Two RCTs compared the use of VP vs. a sham surgery control group. Notably, RCTs comparing nonsurgically treated patients as a control group vs. those undergoing VP uniformly reported that VP contributed to improved pain relief. In contrast, RCTs comparing sham surgery vs. VP uniformly reported no significant differences between the two groups.

Key Words: Placebo effect, randomized-controlled trials, sham-controlled surgery, vertebral compression fractures, vertebroplasty

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BACKGROUND

Vertebral compression fractures (VCFs), typically caused by trauma or osteoporosis, are a major cause of morbidity and disability in the US. There are approximately 750,000 compression fractures reported annually.[13] Approximately 1 in 5 people over the age of 70 or postmenopausal women suffer from symptoms related to VCFs.[5] While most VCFs heal spontaneously within a few months, some patients continue to suffer from pain/disability refractory to conservative therapy (e.g., rest, bracing, activity modification, analgesics, and muscle relaxants).[1]

Vertebroplasy (VP) is commonly employed to treat symptomatic VCFs refractory to conservative treatment. These procedures involve the percutaneous injection of bone cement, usually polymethylmethyacrylate (PMMA), into the fractured vertebral body.[14] Here, we reviewed six well-designed randomized control trials (RCTs) (2009–2015) to better determine the safety/efficacy of this treatment for symptomatic VCF. Four RCTs compared the results of VP to nonsurgically treated control groups, while two studies compared sham procedures (no VP performed) vs. VP. Of interest, the four RCTs demonstrated significant improvement in pain for those undergoing VP vs. control patients, while there were no differences in outcome for the two RCT studies evaluating sham surgery vs. VP.

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RANDOMIZED CONTROLLED TRIALS

We identified four RCTs that compared VP to medical treatment. Inclusion and exclusion criteria as well as findings from these studies can be found in Table 1. Key results from these studies are summarized below.

The VP in the acute osteoporotic vertebral compression fractures (Vertos II) trial was an RCT involving five centers in the Netherlands and one in Belgium that randomized symptomatic VCF patients to VP vs. no surgical treatment.[11] There were multiple inclusion criteria [Table 1]. The primary end point was pain relief

Table 1: Vertebroplasty vs. nonsurgical management

First author	Klazen *et al.*[11]	Farrokhi *et al.*[7]	Blasco *et al.*[2]	Chen *et al.*[4]
Inclusion Criteria	1) Age >50 2) VCF at T5 or below 3) Back pain of >5 on a visual analogue scale (VAS) for <6 weeks 4) Osseous edema on MRI 5) Focal tenderness at fracture level	1) VCF with 10-70% loss of vertebral height 2) Medically refractory pain of >4 weeks but <1 year 3) Focal tenderness related to VCF 4) Radiographic evidence of osteoporosis and VCF	1) Acute or painful VCF from T4-L5 with clinical onset <12 months 2) Radiographic evidence of VCF on spine radiography defined by 20% reduction of vertebral body and presence of edema on MRI or activity on bone scan 3) VAS pain score ≥4	1) Presence of osteoporotic compression spinal fractures on MRI 2) Persistent back pain for at least 3 months
Exclusion Criteria	1) Severe cardiopulmonary comorbidity 2) Coagulopathy 3) Systemic or local spine infection 4) Suspected malignant disease 5) Neurologic symptoms (radiculopathy, cord compression) 6) Inability to tolerate MRI	1) Coagulopathy 2) Local or systemic infection 3) Secondary osteoporosis 4) Inability to inform consent (including dementia) 5) Impaired cardiopulmonary function 6) Morphology of VCF not amenable to VP (e.g., posterior wall defect) 7) Cancer involving the spine 8) traumatic VCF 9) presence of neurologic symptoms	1) Untreatable coagulopathy 2) Active local or systemic infection 3) Concurrent malignancy 4) Fragment of vertebral body causing occupation of vertebral canal 5) Nonosteoporotic VCF 6) Active associated disorders (i.e., spondyloarthropathies or fibromyalgia) 7) Disorders that may interfere with assessment of pain or quality of life (i.e., dementia)	None Provided
Sample Size by Cohort	86 in VP group; 77 in nonsurgical group	40 in VP group; 42 in nonsurgical group	64 in VP group; 61 in nonsurgical group	46 in VP group; 43 in nonsurgical group
Primary Endpoints	1) Pain Relief (VAS)	1) Pain Relief (VAS) 2) Quality of Life (Oswestry lower back pain disability index)	1) Pain relief (VAS) 2) QoL measures (Qualeffo-41)	1) Pain Relief assessed by VAS 2) Functional outcome (ODI).
Key Results	1) Mean VAS score in the VP arm decreased by 5.7 points while the VAS score in the non-surgical arm decreased by 3.7 points ($P<0.0001$) at one year after surgery	1) Reduction in pain score in VP group was significantly higher relative to the non-surgical group at 1 week (5.1 versus 0.8, $P < 0.001$) and this difference remained significant at the 2 and 6-month follow-up. By the 12-month follow-up, the difference in the reduction in pain score was no longer significant between the two arms. 2) The reduction in the Oswestry index was higher in the VP group (difference of 14 points between groups, $P < 0.01$) at the 36-month follow-up.	1) VP had greater short-term reduction in VAS scores compared to conservative management (3.07 versus 1.59, $P = 0.0172$). By 6 months and 12 months, the reduction in VAS scores between surgical treatment group and conservative management were similar. 2) VP group had significant improvements in Qualeffo-41 total score compared to baseline at all time points. Conservative treatment group had statistically significant improvement compared to baseline only at 6 months and 12 months.	1) VP demonstrated statistically significant, greater pain relief than conservative treatment during all follow up intervals (2.5 versus 4.1, $P < 0.001$ at one year). 2) VP had statistically significant greater improvements in ODI scores during all follow up intervals ($P < 0.001$).

measured at 1 month and 1 year, which was assessed utilizing the visual analog scale (VAS) score. A total of 202 patients were enrolled, with 101 randomized to VP and 101 randomized to nonsurgical treatment. At 1 year, 86 completed 1-year follow up in the treatment arm and 77 patients completed follow-up in the control arm. At 1 year, the mean VAS score in the VP arm decreased by 5.7 points whereas the VAS score in the nonsurgical arm decreased by 3.7 points ($P < 0.0001$). The authors concluded that VP was an effective treatment for painful VCF.

Farrokhi *et al*.[7] in a single-institution RCT examined the efficacy of VP for VCF secondary to osteoporosis. There were multiple inclusion and exclusion criteria [Table 1]. A total of 82 patients were randomized; 40 were in the VP group whereas 42 were in the nonsurgical treatment groups. The two arms were well-balanced in terms of demographics and pertinent clinical variables. By the 12-month follow-up, the difference in the reduction in pain score was no longer significant between the two arms. In terms of quality of life (QoL), the reduction in the Oswestry index was higher in the VP group throughout all time points, including the 36-month follow-up. The authors conclude that VP was an effective treatment for VCF related to primary osteoporosis.

Blasco *et al*.[2] described a single-institution RCT investigating the 1-year effectiveness of VP in improving QoL and pain for osteoporotic VCF. There were multiple inclusion and exclusion criteria [Table 1]. The primary outcomes were pain score assessed by VAS and QoL measures using the Quality of Life Questionnaire of the European Foundation for Osteoporosis (Qualeffo-41). A total of 125 patients were randomized; 64 to VP and 61 to the nonsurgical, conservative treatment. VAS scores diminished significantly for both groups compared to baseline. However, by 6 months and 12 months, the reduction in VAS scores between surgical treatment group and conservative management were similar (36% versus 34% reduction and 19% versus 18% reduction). Regarding QoL, the VP group had significant improvements in Qualeffo-41 total score at all time points whereas the conservative treatment group had statistically significant improvement only at 6 months and 12 months. The authors concluded that VP and conservative treatment are both efficacious in improving VAS pain scores and improving QoL, however, VP was found to have significant pain relief and greater QoL improvement at 2 months.

Chen *et al*.[14] conducted a single-center RCT comparing VP with conservative therapy. There were multiple inclusion criteria [Table 1]. The primary outcomes were pain relief assessed by VAS and functional outcome assessed by Oswestry Disability Index (ODI). At the 1-year follow up, however, 46 patients had VP and 43 were treated conservatively. In terms of VAS pain scores, VP demonstrated statistically significant, greater pain relief than conservative treatment during all follow-up intervals (2.5 versus 4.1; $P < 0.001$ at 1 year). Similarly, in terms of functional outcomes, VP had statistically significant greater improvements in ODI scores during all follow-up intervals ($P < 0.001$). The authors concluded that, at 1 year, VP provided greater pain relief and improved functional outcomes compared to conservative therapy.[14]

We identified two RCTs that compared VP to sham surgery. Inclusion and exclusion criteria as well as results from these studies can be found in Table 2. Key results from these studies are summarized below.

The Investigational Vertebroplasty Safety and Efficacy Trial (INVEST) was a multicenter trial that randomized symptomatic VCF patients to receiving VP or sham surgery. There were multiple inclusion/exclusion criteria [Table 2]. A total of 131 patients were enrolled – 68 patients were randomized to VP and 63 patients to the sham surgery group (e.g., all aspects of the surgery were simulated, except for needle insertion into the VCF site). There was no significant difference in either primary end points between the VP group and the sham surgery group.[10] No significant differences between the two groups were reported at the 1-year follow-up in a continuation study.[6] The authors conclude that improvement in pain and pain-related disability were not significantly augmented by VP.

The second sham-controlled RCT explored the efficacy of VP conducted by Buchbinder *et al*.[3] There were multiple inclusion and exclusion criteria [Table 2]. The primary outcome was overall pain, assessed on a scale of 0–10 assessed at 3 months after treatment. A total of 78 patients were enrolled; 38 randomized to VP and 40 to the sham surgery group. No significant differences between the two groups were reported at the 2-year follow-up.[15] The authors conclude that VP provided no beneficial effects relative to sham procedures.

EXPERT COMMENTARY

"All of the positive trials evaluated vertebral augmentation versus medical management. This means that there is a positive effect on pain and quality of life of vertebral augmentation compared to the available treatment alternatives. Since sham procedures are rarely knowingly offered in clinical practice, this in and of itself may be sufficient for payment and policy decisions." Daniel K Resnick, MD, University of Wisconsin.

The authors have done a very nice job in presenting what may seem to be confusing data regarding the efficacy of vertebral augmentation (VA) for osteoporotic compression fractures. When the data is presented side

Table 2: Vertebroplasty vs. sham controlled surgery

First author of RCT	Kallmes *et al.*[10]	Buchbinder *et al.*[3]
Inclusion Criteria	1) Age >50 2) 1-3 VCF between T4 and L5 3) Pain intensity of >3 on a 10 point-scale that is refractory to nonsurgical management 4) VCF <1 year in age	1) 1-2 VCF 2) Pain refractory to non-surgical management 3) Radiographic evidence of compression fracture 4) VCF <1 year in age
Exclusion Criteria	1) Neoplasm as the cause of VCF 2) Spinal canal compromise 3) Concurrent hip fracture 4) Active infection 5) Coagulopathy 6) Surgery within the previous 60 days 7) Incapacity prohibitive of follow-up (e.g., dementia, inability to speak English)	1) >2 VCF 2) Spinal cancer 3) Neurologic deficit or symptoms 4) Osteoporotic VCF with >90% collapse 5) Spinal canal compromise 6) Previous vertebroplasty 7) Inability to give informed consent or likelihood of non-compliance
Sample Size by Cohort	68 in VP group 63 in sham surgery group	38 in VP group 40 in sham surgery group
Primary Endpoints	1) RDQ (Roland-Morris Disability Questionnaire) assessment 2) Report of pain based on a scale of 0-10	1) Overall pain, assessed on a scale of 0-10 assessed at 3 months after treatment
Key Results	1) RDQ dropped from 16.6 to 12.0 in the VP group and dropped from 17.5 to 13.0 in the sham surgery group at one month, $P=0.49$ 2) Pain score dropped from 6.9 to 3.9 in the VP group and 7.2 to 4.6 in the control group, $P=0.19$	1) At the three-month follow-up, the mean pain score dropped by 2.6 points in the VA group and 1.9 points in the sham-surgery group, this difference was statistically significant.

by side, as it is in the paragraphs above, several themes emerge which make the picture substantially less cloudy. First, all of the positive trials evaluated VA versus medical management. This means that there is a positive effect on the pain and QoL of VA compared to the available treatment alternatives. Since sham procedures are rarely knowingly offered in clinical practice, this in and of itself may be sufficient for payment and policy decisions. Also, three of four positive studies required magnetic resonance imaging (MRI) evidence of edema and two of the four required point tenderness over the fracture in order to be included in the study. These requirements likely helped target those who would likely benefit from the procedure, i.e., patients with subacute but nonhealing fractures which were likely the source of the pain. In contrast, neither of the negative studies required evidence that the compression fracture treated was an active source of pain, meaning that patients with healed fractures and chronic back pain were more likely included. In this population, VA is less likely to be effective and sham procedures, similar to those used commonly for the management of chronic back pain (anesthetic injection), may be somewhat effective.

In short, the differences in results seen in the positive and negative studies are quite easily explained by inclusion criteria and study methodology. VA is likely effective for rigorously selected patients with subacute pain, focal tenderness, and edema on MRI scans concordant with the level of the fracture. VA is likely not as effective for less rigorously selected patients. Anesthetic injection into the facet is a long-standing pain procedure, and while it may not have substantial long-term efficacy, it certainly can have a short-to-moderate term effect, which may in fact be just as potent as indiscriminately applied VA.

"We continue to advise patients with painful vertebral column fractures to consider vertebroplasty or kyphoplasty in the appropriate setting based not just on exclusion and inclusion criteria but realistic outcome expectations by individual patient." William Taylor, University of California, San Diego

It is difficult to look at treatments objectively that are in routine use around the world by multiple physicians. It would be rare today to find someone who did not routinely refer and or treat patients by VP or kyphoplasty with vertebral column fractures. As such, many of the trials which do not reveal justification for this common treatment are met with skepticism.

The importance of this paper lies in its review of RCTs rather than level 3 or less data, which is more common in many of the larger series. The VERTOS trial is an excellent prospective series that includes MRI data and long-term follow-up, which is critical in elderly patients who can have multiple issues compounding short-term outcomes, and clearly showed improvement in pain for patient's treated with VP as opposed to control group. The second trial by Farrokhi *et al.* demonstrated improvement within the first year of treatment, which then degraded by 2 and 3 years. Adjacent level disease, multiple medical problems, and secondary fractures may play a role in this, however, intervention clearly showed improvement in the short-term outcomes.

In both of the sham surgery trials, there was a tendency towards improvement with VP over sham procedure.

Although it did not reach statistical significance, the consistency of the data suggest that it is an issue of limited number and the limited time frame for follow-up. Given the long-standing history of pain in many of the patient's in these trials, it is not surprising that the trend was present without statistical significance.

Many of the RCTS do not include outcome scales and or preoperative assessment, which are routinely used in clinical practice today. This includes the preoperative screening with MRI scans, specifically reviewing the signal on T1 and tracking sagittal balance or local Cobb angle and treated versus untreated patients. While some of the studies reviewed used MRI criteria, none considered sagittal balance in preoperative, postoperative, and/or outcomes course. The importance of preserving balance and preventing kyphosis should not be underestimated in this patient population.

We continue to advise patients with painful vertebral column fractures to consider VP or kyphoplasty in the appropriate setting, based not just on exclusion and inclusion criteria but realistic outcome expectations by individual patient.

"Put your trust in trials with a sham surgery control arm when interventional treatment is concerned and remain skeptical when only best medical treatment is available for comparison." Peter Warnke, MD, University of Chicago.

Surgery remains the most powerful placebo in Medicine, as so nicely illustrated in this review regarding RCTs on VP in compression fractures. This fact is crucial and makes it difficult to compare the outcomes of surgical intervention relative to those receiving the best medical care. The movement disorder community has realized this early on and drawn the correct conclusions for the design of future trials.[8,9] On-going research is now beginning to uncover the biological basis of the placebo effect mediated via sham surgery and the differential tendency to develop such effects.[12,16] Consequently, the seminal phase III trials on the effects of perilesional stem cell treatment in stroke patients have been designed with incorporation of a sham-surgery control arm.

So, put your trust in trials with a sham surgery control arm when interventional treatment is concerned and remain skeptical when only best medical treatment is available for comparison.

EDITORIAL COMMENTS

Modern medicine thrives on certainty – the certainty of a definitive EKG change indicating an acute myocardial infraction and of pathognomonic findings triggering a pre-determined course of treatment. These paradigms of certainty unravel when applied to the majority of patients afflicted with chronic pain. Daily confrontation with incapacitating discomfort or inconveniences can distort the human psyche in ways that magnify the perceived pain in a self-perpetuating and catastrophic manner. With this in mind, the favorable impacts of VP on select patients' perception of pain are extraordinary. Does the "placebo effect" contribute to the efficacy of VP? Almost certainly. The question is, how much does it contribute. The reality is that we may not be able to rigorously answer this question – since any novel intervention will be compared to medical management including pain medicines that were never compared to "sugar" pills. The two RCTs with sham surgical controls does suggest that the physiologic effects of VP in terms of pain relief in some patients with compression fracture may not be as great as those suggested by the four positive RCTs. Whether the differences between these trial results are due to patient selection or contribution from the "placebo effect" remains an open question. However, it is hard to argue that VP should not be offered to select patients based on this RCT literature. As a final consideration, it is important to recognize that opioid abuse has emerged as a major epidemic in recent years. VP and other surgical management strategies aimed to minimize the need for opioid use warrant consideration in this context.

REFERENCES

1. Alexandru D, So W. Evaluation and management of vertebral compression fractures. Perm J 2012;16:46-51.
2. Blasco J, Martinez-Ferrer A, Macho J, San Roman L, Pomes J, Carrasco J, *et al*. Effect of vertebroplasty on pain relief, quality of life, and the incidence of new vertebral fractures: A 12-month randomized follow-up, controlled trial. J Bone Miner Res 2012;27:1159-66.
3. 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.
4. Chen D, An ZQ, Song S, Tang JF, Qin H. Percutaneous vertebroplasty compared with conservative treatment in patients with chronic painful osteoporotic spinal fractures. J Clin Neurosci 2014;21:473-7.
5. Cohen LD. Fractures of the osteoporotic spine. Orthop Clin North Am 1990;21:143-50.
6. Comstock BA, Sitlani CM, Jarvik JG, Heagerty PJ, Turner JA, Kallmes DF. Investigational vertebroplasty safety and efficacy trial (INVEST): Patient-reported outcomes through 1 year. Radiology 2013;269:224-31.
7. 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.
8. Freeman TB, Vawter DE, Leaverton PE, Godbold JH, Hauser RA, Goetz CG, *et al*. Use of placebo surgery in controlled trials of a cellular-based therapy for Parkinson's disease. N Engl J Med 1999;341:988-92.
9. Gross RE, Watts RL, Hauser RA, Bakay RA, Reichmann H, von Kummer R, *et al*. Intrastriatal transplantation of microcarrier-bound human retinal pigment epithelial cells versus sham surgery in patients with advanced Parkinson's disease: A double-blind, randomised, controlled trial. Lancet Neurol 2011;10:509-19.
10. Kallmes DF, Comstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, *et al*. A randomized trial of vertebroplasty for osteoporotic spinal fractures. N Engl J Med 2009;361:569-79.
11. Klazen CA, Lohle PN, de Vries J, Jansen FH, Tielbeek AV, Blonk MC, *et al*. Vertebroplasty versus conservative treatment in acute osteoporotic vertebral

compression fractures (Vertos II): An open-label randomised trial. Lancet 2010;376:1085-92.
12. Ko JH, Feigin A, Mattis PJ, Tang CC, Ma Y, Dhawan V, *et al*. Network modulation following sham surgery in Parkinson's disease. J Clin Invest 2014;124:3656-66.
13. Melton LJ, 3rd, Thamer M, Ray NF, Chan JK, Chesnut CH, 3rd, Einhorn TA, *et al*. Fractures attributable to osteoporosis: Report from the National Osteoporosis Foundation. J Bone Miner Res 1997;12:16-23.
14. Predey TA, Sewall LE, Smith SJ. Percutaneous vertebroplasty: New treatment for vertebral compression fractures. Am Fam Physician 2002;66:611-5.
15. Staples MP, Howe BM, Ringler MD, Mitchell P, Wriedt CH, Wark JD, *et al*. New vertebral fractures after vertebroplasty: 2-year results from a randomised controlled trial. Arch Osteoporos 2015;10:229.
16. Tetreault P, Mansour A, Vachon-Presseau E, Schnitzer TJ, Apkarian AV, Baliki MN. Brain Connectivity Predicts Placebo Response across Chronic Pain Clinical Trials. PLoS Biol 2016;14:e1002570.