Editorial

Does the VAPOUR trial shed new light on the efficacy of vertebroplasty for acute painful osteoporotic fractures?

Fady Y. Hijji, Ankur S. Narain, Krishna T. Kudaravalli, Kelly H. Yom, Kern Singh

Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, IL, USA

Correspondence to: Kern Singh, MD. Professor, Department of Orthopaedic Surgery, Rush University Medical Center, 1611 W. Harrison St, Suite #300, Chicago, IL 60612, USA. Email: kern.singh@rushortho.com.

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As the population of the United States ages, the incidence of osteoporosis and associated complications will continue to rise (1). Up to 750,000 cases of vertebral fracture occur annually, with incidence rates in elderly women approaching 1% per year (2,3). Osteoporotic vertebral fractures are a common source of significant morbidity and disability in elderly populations (4). Back pain, spinal deformities, and substantial reductions in quality of life are common consequences of osteoporotic vertebral fractures (5). Standard treatment for this pathology consists of conservative management including physical therapy, anti-osteoporosis pharmacotherapy, analgesia, and bracing. Although conservative management is typically successful, certain subsets of patients will fail to improve with non-operative therapy. Consequently, these patients may experience long term disability, increased frequency of hospitalization, and requirements for additional care (5).

Vertebroplasty has become a popular method to provide pain relief and potentially improve outcomes in these patients (6). However, there has been inconsistent data to support the superiority of vertebroplasty over conservative management (1,7,8). Two previous multicenter, double-blind, randomized controlled trials have demonstrated no beneficial effect of vertebroplasty when compared to placebo (7,8). However, the populations utilized in these studies included patients receiving interventions up to 1 year after experiencing a vertebral fracture.

Clark *et al.* attempted to emulate these studies, with particular focus on the effects of vertebroplasty as an early intervention (9). The inclusion criteria for patients recruited to this study were age greater than 60 years, back pain of less than 6 weeks' duration, and a Numeric Rating Scale (NRS) pain score ≥7. Following screening, 120 patients were enrolled and randomized to receive either a vertebroplasty or placebo procedure. The primary outcome was the percent of patients exhibiting an NRS score ≤4 at 14 days following the intervention. Secondary outcomes consisted of other patient-reported outcome questionnaires, including the Roland-Morris Disability Questionnaire (RDQ), the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO), the European Quality of Life-5 Dimensions (EQ-5D), and the Visual Analog Scale (VAS) for pain. Interestingly, the authors determined that undergoing vertebroplasty was associated with greater improvements in NRS at all follow-up time points up to 6 months, contrary to the findings from previous studies.

The study performed by Clark *et al.* exhibits a few strengths. The study is of high quality, as it was performed as a prospective, double-blind randomized controlled trial. This characteristic permits for an accurate comparison between vertebroplasty and the standard, conservative therapy. Additionally, the study assessed the efficacy of the blinding process by having patients fill out a questionnaire to identify whether they believe they received the placebo or vertebroplasty intervention, as well as to rate the confidence and reasoning behind their guess. This process is similar to that utilized in the study performed by Kallmes *et al.* (8). The authors also assessed blinding within the data collectors by requiring them to fill out the same questionnaire for each

patient. In addition to assessing the quality of the blinding process, the questionnaire also provides an alternative method to identify a patient's perception of their treatment and its effects. One aspect of this study that improved on the previously performed trials was its lack of patient crossover between treatment interventions. This allowed for a more accurate representation of the treatment effects during each follow up time point.

Despite these strengths, this study demonstrates multiple intrinsic limitations. The study was performed as a multicenter trial; however, only 8.3%, 6.7%, and 0.8% patients were recruited in total from the three other study sites. There is also no information regarding how many of those excluded at any of the follow-up time points were from these three sites. This brings into question the power and generalizability of the study findings. Additionally, the authors utilized a study population undergoing a mixture of inpatient and outpatient vertebroplasty. This highlights substantial variability in the severity of disability between patients, limiting the strength of the study conclusions. Moreover, there is no recording of patient comorbidity through any standardized scoring metric, such as the Charlson Comorbidity Index (CCI) or American Society of Anesthesiologists' (ASA) score. This makes it difficult to identify the general health of the population or to assess any differences in comorbidity burden between cohorts.

Many of the analyses within the study are also inherently flawed or simply missing. The authors recorded and reported the distribution for a variety of patient demographics and disease characteristics. However, there is no report of any statistical comparison of these demographics between the cohort populations. Not only are analyses regarding the baseline differences not reported, these potential confounding variables are not adjusted for in the comparisons of primary and secondary outcomes. Similarly, the authors also failed to report any adjustments within the subgroup analyses performed for surgical region and duration of fracture. This limits the ability to attribute differences in outcomes to the intervention itself. Additionally, all of the analyses performed only provide "risk differences", simply reporting the difference in the percentages of those achieving the primary outcome in both cohorts. This outcome is not meaningful, as this it does not supply any information regarding the treatment effect of vertebroplasty. Rather, the authors should have provided odds ratios or relative risks for these analyses, as this would assist in the interpretation of the benefit of the treatment compared to placebo. Finally, the power of these analyses remains in question. Most of the subgroup analyses have a limited number of patients achieving the primary outcome, limiting the authors' ability to provide any significant conclusions regarding these groups.

The clinical value of Clark *et al.*'s study may be limited. The previously performed randomized controlled trials by Kallmes *et al.* and Buchbinder *et al.* identified no differences in outcomes following control and vertebroplasty treatments for osteoporotic vertebral fractures; however, the study populations consisted of patients presenting early and late following the onset of their symptomology (7,8). One of the primary reasons for performing this study was to identify whether early intervention with vertebroplasty improves patient outcomes compared to conservative management. However, to strengthen the conclusions, especially in the setting of conflicting findings to these previous studies, the present study should have also compared early intervention to late intervention. Both previous studies were able to perform subgroup analyses with patients undergoing early intervention, maintaining the result that no benefit was achieved with vertebroplasty compared to placebo treatment. However, the patient population in the present study only includes those receiving early intervention, thus not allowing for this separate analysis. As such, it is difficult to conclude that it is the early intervention itself that caused the conflicting results, especially in combination with the methodological flaws mentioned previously. The authors also attempt to supplement their clinical findings with radiographic data. However, their measurements relied simply on vertebral height of the affected vertebral bodies. This also has limited utility, as the polymethylmethacrylate (PMMA) used in the vertebroplasty can substantially impact the radiographic interpretation due to its radiopaque qualities.

The study by Clark *et al.* did improve on a few of the limitations exhibited in previous randomized controlled trials investigating vertebroplasty. However, the flaws of this study significantly limit its ability to provide any substantial conclusions regarding the efficacy of vertebroplasty for osteoporotic vertebral fractures. The previously performed double-blind, randomized controlled trials appear to be of superior methodological quality, bringing into question the conflicting findings of the study by Clark *et al.* Further investigations with larger sample sizes and improved analytic and recruitment methods are necessary to overcome many of the limitations of this study.

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