AJNR

# VERTOS: A Step in the Right Direction

Jeffrey G. Jarvik and William Hollingworth

*AJNR Am J Neuroradiol* 2007, 28 (3) 561-562
http://www.ajnr.org/content/28/3/561

COMMENTARY

# VERTOS: A Step in the Right Direction

The authors of VERTOS are to be congratulated on performing a randomized controlled trial investigating percutaneous vertebroplasty.[1] To the practitioners of vertebroplasty, the results should be comforting but not surprising—there is now evidence from a randomized controlled trial that vertebroplasty provides short-term pain relief and results in less disability than conservative management. Although there is no such thing as a perfect study, with every study (but probably most importantly randomized controlled trials), the methods need to be carefully scrutinized to have confidence that the conclusions are valid. Policy makers, insurers, primary care physicians, and patients are likely to look at the data critically and ask if there were fatal flaws in the study design, and, most fundamentally, if the data show that percutaneous vertebroplasty is beneficial to patients in the long term. As is frequently the case in both science and life, the answers are complex.

Regarding the validity of the results of a randomized controlled trial, the main questions to ask are the following: 1) Was the therapy assigned in a truly random fashion? 2) Was the randomization scheme concealed from both subjects and investigators? 3) Were all patients who entered the trial accounted for at the conclusion? 4) Were the subjects analyzed according to the group to which they were assigned (an intention-to-treat analysis)? I shall address these issues point by point.

Was therapy assigned in a random fashion and was the assignment scheme concealed? The authors do not fully address this issue. They state that the patients were randomized by an independent central operator but do not state how the assignments were generated. Presumably a random process such as a computerized random number generator was used to produce the assignments, but this should have been explicitly stated. The authors get all the points for concealment by having an independent central operator do the assignments (presumably by telephone).

The authors do worse on the next 2 points. Randomized controlled trials are considered the gold standard of clinical research because patient characteristics, measured and unmeasured, which influence outcome, will, on average, be evenly represented in the treatment arms of the trial. This depends entirely on the investigators analyzing all subjects according to their initial treatment assignment. If subjects are not equally followed up, a potential selection bias is introduced. The authors note that 8 of 46 (17%) subjects who were enrolled and randomized declined the randomly assigned therapy and were dropped from the analysis. Although this may seem high, in fact for surgical trials, nonadherence rates such as these are not uncommon. Rather than dropping the subjects from the study, the authors should have continued to follow them and analyze their data as though they had received the treatment to which they were randomly assigned. This is what is meant by intention-to-treat analysis.[2] Four (9%) additional subjects did not fill out the 2-week questionnaire. However, their baseline and 1-day outcomes should still be included in the report. Sackett et al[3] suggested that if more than 20% of subjects are not followed to the conclusion of a trial, the results are likely not valid and some journals such as *Evidence-Based Medicine* would not publish trials with less than 80% follow-up rates.

Another issue that is not clear from the article is if subjects who had a prior vertebroplasty were excluded from the trial. Presumably patients who returned for a 2nd (or 3rd or 4th) vertebroplasty had a good outcome after the first one compared with patients who did not return for a subsequent procedure. Because patient expectations are a powerful predictor of outcome,[4] if the authors did not exclude those who had a previous vertebroplasty, they were potentially biasing their results in favor of the procedure.

For these reasons, the validity of the VERTOS study results is questionable. What if we determined that the study had strong validity? Would we be convinced by the trial data that percutaneous vertebroplasty is beneficial to patients in the long term?

At 1-day postprocedure, the mean pain scores improved by 2.3 points (32%) from a baseline of 7.1 in patients treated with percutaneous vertebroplasty. However, another way of looking at the data is the proportion of subjects who attained a 50% reduction in pain. A review by McQuay and Moore[5] cites response rates due to placebos between 7% and 49% for patients with acute and chronic painful conditions. In 1 large study of 12,000 patients with postoperative pain, the placebo response rate was 18%. McQuay and Moore point out that in smaller trials of 100 subjects, anywhere from 0%–50% of subjects could be expected to achieve 50% pain reduction by chance alone.

In the 1 patient who had a documented vertebroplasty complication (a pedicle fracture), the pain was relieved by anesthetic infiltration of the pedicle. It is impossible to know how many other patients treated with percutaneous vertebroplasty received pain relief due to the anesthetic rather than the cement stabilization of the vertebra. Two ongoing randomized controlled trials, one in the United States headed by David Kallmes, MD, funded by the National Institutes of Health, and the other in Australia, headed by Rachel Buchbinder, PhD, should resolve this uncertainty; both compare percutaneous vertebroplasty to a control intervention consisting of an anesthetic injection.

There have been only 2 other published controlled (nonrandomized) trials of vertebroplasty: 1 by Diamond et al[6] and Diamond and Clark[7] and the other by Alvarez et al.[8] Both of these trials showed an immediate and short-term benefit that was not sustained through 6 months. In the current study, by 2 weeks, the difference in pain scores was not statistically significant, though differences in disability, measured by the Roland-Morris Questionnaire, persisted.

The use of medication as an outcome is problematic, given that the control group intervention was mostly a review and increase of medications. Moreover, the 1-point increase in medications in the control group on day 1 is not likely to reflect any increase in pain that has been ongoing for 6 weeks to 6 months.

Supported by the Royalty Research Fund, University of Washington, and in part by Grants # P60-AR48093–01 from National Institute for Arthritis and Musculoskeletal and Skin Diseases

The authors note that 2 patients treated by percutaneous vertebroplasty had subsequent fractures at adjacent levels. The authors then repeated the analysis, excluding these 2 subjects and found a statistically significant difference. By systematically excluding the subjects who did worse, the authors again introduced a bias into their analysis. Although it is fine to describe why subjects might have poor outcomes following percutaneous vertebroplasty, it is not acceptable to exclude the subjects with worse outcomes in a formal comparison. This issue is particularly important because percutaneous vertebroplasty subjects may be at higher risk for subsequent fractures. Because the sample size is small, it is difficult to judge the significance of 2 subsequent fractures in the percutaneous vertebroplasty group, but it begs the question of whether there were any subsequent fractures in the conservatively treated group.

Unfortunately, the VERTOS study does not let us conclude that vertebroplasty provides a long-term benefit for patients. However, the authors do leave us with hope for the future—the VERTOS II trial.

The design of any randomized controlled trial needs to include an a priori power analysis to determine if the sample size will be adequate to minimize the chance of a type-2 error (accepting the null hypothesis when it is false). In the current study, the authors do not discuss why they choose to randomize 46 patients. Neither do they describe the primary hypothesis being tested. Was their study designed to examine primarily pain, functional status, disability, or medication use? Without clearly defining their hypothesis and justifying their sample size, the authors leave the readers wondering how and when these decisions were made. Because there is a VERTOS II trial currently recruiting (www.clinicaltrials.gov) with a sample-size target of 200 subjects, presumably the reason that sample-size calculations were not discussed in this article is that VERTOS was a pilot study designed to gather data on response rates and variability, to allow sample-size calculations for the larger VERTOS II trial.

Much can be forgiven in pilot studies, including small sample sizes and exploration of datasets without clearly defined primary hypotheses. The authors of VERTOS are to be complimented on their desire to gather rigorous randomized controlled trial data about a procedure that many in the radiologic community believe has progressed beyond equipoise into the realm of near certainty for the existence of a clinical benefit.[9] Only time will tell if VERTOS II, which began in 2005 and is slated for completion in 2008, will answer many of the questions raised by VERTOS. However, without a well-designed randomized controlled trial, the only certainty is that uncertainty will continue.

## References


1. Voormolen MJH, Mali WPTM, Lohle PNM, et al. **Percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures. The VERTOS study.** *AJNR Am J Neuroradiol* 2007;28:*****
2. Hollis S, Campbell F. **What is meant by intention to treat analysis? Survey of published randomised controlled trials.** *BMJ* 1999;319:670–74
3. Sackett D, Rcihardson W, Rosenberg W, et al. *Evidence-Based Medicine: How to Practice and Teach EBM***.** New York: Churchill Livingstone; 1997
4. Lutz GK, Butzlaff ME, Atlas SJ, et al. **The relation between expectations and outcomes in surgery for sciatica.** *J Gen Intern Med* 1999;14:740–44
5. McQuay HJ, Moore RA. **Placebo**. *Postgrad Med J* 2005;81:155–60
6. Diamond TH, Bryant C, Browne L, et al. **Clinical outcomes after acute osteoporotic vertebral fractures: a 2-year non-randomised trial comparing percutaneous vertebroplasty with conservative therapy.** *Med J Aust* 2006; 184:113–17
7. Diamond TH, Clark WA. **Percutaneous vertebroplasty: a novel treatment for acute vertebral fractures.** *Med J Aust* 2001;174:398–400
8. Alvarez L, Alcaraz M, Perez-Higueras A, et al. **Percutaneous vertebroplasty: functional improvement in patients with osteoporotic compression fractures.** *Spine* 2006;31:1113–18
9. Wagner AL. **Vertebroplasty and the randomized study: where science and ethics collide.** *AJNR Am J Neuroradiol* 2005;26:1610–11



Jeffrey G. Jarvik
William Hollingworth
*Department of Radiology*
*University of Washington*
*Seattle, Washington*