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Society of Interventional Radiology Commentary on Vertebroplasty and the August Studies in the New England Journal of Medicine

The Aug. 6 edition of the New England Journal of Medicine contained two randomized controlled studies that have created a controversy regarding treatment of symptomatic vertebral body compression fractures. Although well intentioned and—for the most part—well performed, these are difficult studies to accomplish. Several important factors need to be considered prior to accepting these two studies as fact negative (that vertebroplasty is no better than a sham control in relieving pain in patients with symptomatic compression fractures). Evidence-based medicine is a hierarchal pyramid with randomized controlled studies at the pinnacle. Throughout the history of medicine, many treatments that were considered effective and the standards of care were subsequently demonstrated through randomized controlled trials to be ineffective, and the standards justifiably changed. Kallmes and Buchbinder should be applauded for performing these studies. The results of these trials are discordant with the more than 15 years of accumulated medical literature espousing the benefits of vertebroplasty; many of these were large prospective trials. Hundreds of thousands of patients have greatly benefited from vertebroplasty with almost complete resolution of their pain. Tens of thousands of patients on intravenous narcotics have been discharged from the hospital virtually pain free following their treatment. Because the Kallmes and Buchbinder studies are so discordant with the body of literature and personal experience of most physicians who treat patients with painful compression fractures, closer scrutiny of the two studies is warranted.

Kallmes, et al., demonstrated no significant difference between vertebroplasty and a sham operation in a randomized, blinded multicenter trial with less than half of the patients enrolled in U.S. centers. The study protocol initially called for 250 subjects, but only 131 subjects were enrolled, with 68 in the vertebroplasty group and 63 in the control group. The trial screened 1,813 patients and excluded 1,682 for various reasons—introducing significant selection bias into the study. Screening MRIs and/or bone scans were not required for patients with known fractures under one year of age. Theoretically, some patients could have a healed fracture and another etiology for their acute pain that was not appropriately treated. One could argue that this would work out during the randomization process; however, the overall sample size was small and the possibility exists that the vertebroplasty arm contained a larger number of such patients. In addition, if patients were treated who had no likelihood of responding to vertebroplasty, it will make the outcomes from vertebroplasty resemble those from a sham procedure even if equal numbers are treated in each group.

Three patients were lost to follow-up at one month, leaving 67 in the vertebroplasty group and 61 in the sham control group—for a total of 128 patients analyzed. The *p* value of 0.06 was obtained by comparing the response rate in the two groups based on these 128 subjects: 64 percent (43/67) vertebroplasty group versus 48 percent (29/61) control group. If the number of patients enrolled had been the targeted level (250) and the percentages of patients with favorable and unfavorable responses had remained the same, the *p* value would be 0.01 (vertebroplasty: 64 percent=80/125 versus control: 48 percent=60/125). Also, if a single additional patient had a favorable response in the vertebroplasty group, then the *p* value would be 0.04. Conversely, if a single additional patient had an unfavorable response in the control group, then the *p* value would also be 0.04.

The Kallmes study allowed patients to cross over to the other treatment after one month. Only eight patients (12 percent) in the vertebroplasty group crossed over to the sham procedure; 27 patients (43 percent) in the sham group crossed over to the vertebroplasty group. The tremendous crossover rate speaks for some obvious benefit of vertebroplasty over sham and is worthy of a future adequately powered analysis to evaluate.

Buchbinder, et al., performed a multicenter, randomized, double-blind, placebo-controlled trial, enrolling patients with one or two painful osteoporotic compression fractures of less than 12 months' duration and unhealed as determined by MRI. Of 219 eligible patients, only 78 were enrolled and were

randomly assigned to a study group (38 to the vertebroplasty group, 40 to the placebo group). Selection bias is likely when only 36 percent of eligible patients are enrolled.

Multicenter trials reduce bias that may come from a single trial site. While the Buchbinder study was a multicenter trial, more than 67 percent of the patients came from a single site and the procedures were performed by a single radiologist. The influence of the single site is likely to be dramatic, and if the primary investigator at the site were in favor of conservative management, then the results could be negatively biased against vertebroplasty.

The mean volume of PMMA injected into the vertebrae was 2.8 cubic centimeters (cc). This is significantly lower than usually injected and reported in other trials and may contribute to the lack of clinical significance between groups.

We recognize the value of randomized controlled trials and evidence-based medicine. But based on the above-discussed weakness in the studies and the degree of discordance between the outcomes of these studies, prior studies and experience, we believe it is premature—and possibly incorrect—to conclude that vertebroplasty is no better than a control sham procedure (trigger point, facet injection). We suggest waiting for the results of the VERTOSS 2 trial to be published and encourage larger clinical trials to address the weaknesses of the two New England Journal of Medicine articles.

In the meantime, patients and providers should be made aware of the data to date for informed consent and of the trials that are ongoing.