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Trials of Vertebroplasty for Vertebral Fractures

TO THE EDITOR: In the August 6 issue, Kallmes et al. report on the Investigational Vertebroplasty Safety and Efficacy Trial (ClinicalTrials.gov number, NCT00068822), and Buchbinder et al. report on a randomized trial of vertebroplasty for painful osteoporotic vertebral fractures (Australian New Zealand Clinical Trials Registry number, ACTRN012605000079640). We have serious concerns about both trials, which included patients with a duration of pain of up to 12 months. Vertebroplasty provides internal fixation of nonhealed osteoporotic vertebral fractures. It is well established that fixation of acute fractures elsewhere in the skeleton reduces fracture pain. Internal fixation of healed fractures is clearly inappropriate. Osteoporotic vertebral fractures usually heal within 8 weeks, although magnetic resonance imaging shows that edema persists longer. The study by Kallmes et al. involved outpatients exclusively, so that inpatients hospitalized with acute fracture pain were excluded. Furthermore, the protocol mandated 4 weeks of medical therapy before enrollment. This protocol effectively removed the entire population of patients with subacute fractures, resulting in a study on healed fractures. A more appropriate selection criterion would have been uncontrolled pain for less than 6 weeks. In the trial reported on by Buchbinder et al., the number of patients with pain for less than 6 weeks was far too small for a subgroup analysis.

The trial by Buchbinder et al. had a target enrollment of 200 patients, but 78 were enrolled over 4 years, substantially limiting statistical power. Although the study is described as a multicenter trial, two of the four hospitals withdrew early from the study, after enrolling five patients each. A total of 68% of the procedures were performed in one hospital by one radiologist. The rates of eligible patients who declined to participate were 64% in the trial reported on by Buchbinder et al. and 70% in the trial reported on by Kallmes et al. (85% in the United States), raising further concerns regarding patient selection.

Neither of these articles can accurately comment on the role of vertebroplasty in the control of subacute osteoporotic fracture pain. In Australia, this is the most common reason for the procedure.

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Dr. Clark reports serving as an investigator in the trial reported on by Kallmes et al. and being a member of the advisory panel for vertebroplasty for the Australian Medicare Services Advisory Committee in 2004 and serving on the panel again in late 2009. Drs. Lyon and Burnes report serving as investigators in the trial reported on by Buchbinder et al. and receiving consulting fees from Cook Medical, which manufactures vertebroplasty products. No other potential conflict of interest relevant to this letter was reported.

rationale, objectives and design of a multicentre randomized controlled trial. Trials 2007;8:33.

TO THE EDITOR: Although the studies reported on by Kallmes et al. and Buchbinder et al. are invaluable additions to research in interventional radiology, we are concerned about the conclusions that may be drawn from them, with the consequence that tens of thousands of patients may be denied a procedure that the vast majority of studies published to date have supported.

First, patients with maximal back pain tend to have the greatest improvement in pain score after vertebroplasty. Unfortunately, these patients would also be the least likely to participate in such studies and to risk being randomly assigned to the placebo group, as evidenced by the pre-procedural pain scores among patients who were enrolled.

Second, neither study was sufficiently powered to perform subanalyses. We have found that patients with certain types of fractures (e.g., those with gas-filled clefts and pathologic fractures) are more likely to have improvement in pain scores after vertebroplasty. The studies were either underpowered to evaluate these subgroups of patients (in the case of patients with fractures with clefts) or excluded them altogether (in the case of patients with pathologic fractures). Certainly, we would not advocate vertebroplasty in all patients with back pain due to compression fractures.

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Dr. Munk reports receiving lecture fees from Cook Medical. No other potential conflict of interest relevant to this letter was reported.

TO THE EDITOR: Conclusions regarding the clinical usefulness of vertebroplasty should be weighed against the limitations of the studies reported on by Buchbinder et al. and Kallmes et al. First, there is the dilemma of whether a group of patients who receive an injection of an anesthetic should be considered a true control, since delivery of a local anesthetic can have beneficial effects for a period exceeding the activity of the drug. Second, the natural history of an uncomplicated vertebral compression fracture is short; it usually resolves by 6 weeks. Only 32% of subjects in the study reported on by Buchbinder et al. and 44% of the subjects in the study reported on by Kallmes et al. were treated within this time frame. Given the short-term follow-up, the influence of an already healed fracture, a spontaneous recovery rate, or another source of pain should be considered. Perhaps most troubling is the significant difference in crossover rates between the treatment and control groups (12% vs. 43%) in the study by Kallmes et al. This difference suggests patient dissatisfaction with the sham procedure that was not fully captured by pain scales.

Given the compelling mechanistic context behind vertebroplasty and widespread patient satisfaction, careful study design, analysis, and long-term outcomes are necessary before this well-established technique can be dismissed.

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TO THE EDITOR: The randomized, controlled trials reported on by Kallmes et al. and Buchbinder et al. show no short-term or medium-term benefit of vertebroplasty for the treatment of symptomatic osteoporotic vertebral fractures, as compared with a single administration of a local anesthetic. We were therefore puzzled that the accompanying editorial recommended that physicians discuss the option of vertebroplasty with their patients to allow the latter to make a choice that is “based on their values and preferences.”

We suggest that it is neither appropriate nor ethical to offer to our patients an intervention that is no more effective, is more expensive, and is possibly more dangerous than a placebo.

The history of vertebroplasty should remind us (again) to be cautious in embracing treatments for which the evidence of efficacy is restricted to anecdote or observation. Empirical confirmation (or refutation) of that which is observed should always be sought. The results of these random-
ized trials should lead to the prompt discontinuation of an ineffective therapy.

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DR. BUCHBINDER AND COLLEAGUES REPLY: Personal anecdote and observational studies are biased toward overestimating treatment benefits for many reasons.1 Randomized, controlled trials are the only truly valid means of establishing or refuting the efficacy of vertebroplasty. Our negative results are supported by the findings of an open randomized trial that did not show any benefit of vertebroplasty over usual care at 3 months.2 All participants in this trial had symptoms for 8 weeks or less, further refuting the contention that benefits are more likely if the treatment is given early.

As stated in our article, our trial was more than adequately powered to achieve its primary efficacy aim of detecting a 2.5-unit advantage of vertebroplasty over placebo with respect to the pain score. Since the mean effect of vertebroplasty has consistently been shown to be close to zero in three randomized trials in which participants in both treatment groups had improvement over time, it is doubtful that there would be subgroups of patients who would benefit from the procedure.3 The only way that a proportion of patients could receive a large benefit from vertebroplasty would be if the condition of another subgroup of patients became much worse, a scenario that does not reflect the available data.

The decision by one center to withdraw from the trial once government approval for reimbursement became available does not diminish the validity of our trial. The other center did not formally withdraw and contributed patients over the first 2 years. Participation rates of 36% of eligible patients in our trial and 30% of eligible patients in the trial reported on by Kallmes et al. are considered more than acceptable by usual trial standards, particularly since both trials included a sham procedure. Participants in both trials were typical of patient populations seen in routine care, and they also shared comparable baseline characteristics, including levels of pain and disability, with participants in other vertebroplasty studies. As indicated by the stringent selection criteria in both trials, all enrolled patients had, by definition, unhealed “acute” or “subacute” vertebral fractures.

Our trial and the trial reported on by Kallmes et al. provide the best evidence we have to date regarding the efficacy of vertebroplasty for osteoporotic vertebral fractures. Vertebroplasty appears to confer no benefit over a sham procedure (withstanding the receipt of local anesthesia) or over usual care, and it poses some risk. We concur with Grey and Bolland that it would be neither appropriate nor moral to offer this treatment in routine care.

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DR. KALLMES AND COLLEAGUES REPLY: With regard to the issue of acute fracture raised by Clark et al.: two controlled studies that compare vertebroplasty in acute fractures with medical therapy showed no benefit of the procedure at follow-up between 6 and 12 weeks.1,2 This lack of benefit may reflect the benign natural history of most fractures. Vertebroplasty is most appropriately performed in patients in whom a course of medical therapy has failed; the duration of this medical therapy varies, but historically it has ranged from 4 to 6 weeks. These persistently painful, edematous fractures, such as those in the patients enrolled in our trial, may be the ideal fracture type in patients in a trial; these fractures have not healed and thus probably have a less benign natural history than an acute fracture.

Baerlocher et al. suggest that we enrolled patients with less severe pain than patients in other trials. This is false. The baseline pain and dis-
ability in our patients were equivalent not only to all other available, controlled augmentation trials,\textsuperscript{1,2,3} but also to an eligible but nonenrolled cohort at our lead site.\textsuperscript{4} We would also caution that enrollment of only patients with the most severe pain might lead to an exaggeration of regression toward the mean, blunting any treatment effect. This tendency may explain the equiv­alent outcome in the trial of treatment for acute fracture reported on by Rousing et al.\textsuperscript{2}

Regarding subtypes of fracture other than the acute and severely painful ones described above, there remains neither consensus nor compelling data to indicate that enrollment only patients with fractures with clefts will lead to a positive outcome in future trials. Not only will such limitations markedly prolong future studies by limiting the number of eligible patients, but the presence of clefts often is noted only with infusion of cement,\textsuperscript{5} rendering randomization based on the presence of cleft imperfect. Further, will there be some threshold for the size of the cleft needed for enrollment? How will this threshold be determined?

Finally, numerous potential confounding variables may have affected crossover. However, crossover was not a prespecified end point. In any case, since nearly all crossovers occurred after 30 days, crossover did not affect our primary conclusion that there were no important differences in outcomes between the vertebroplasty and control groups at 1 month.

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Since publication of the article, Dr. Kallmes reports serving as a consultant for Skeltex. No further potential conflict of interest relevant to this letter was reported.


THE EDITORIALIST REPLIES: We should discon­tinue a treatment when there is convincing ev­idence that it yields little effect. Unless policies are changed so that reimbursement is denied for these procedures, doctors will still offer and perform vertebroplasty despite what the data sug­gest. In both studies, controls were active and, in fact, they may have been responsible for under­estimation of the true treatment effect. When there is a paucity of level 1 evidence, as in approx­imately 50% of health care diagnostic and treatment decisions, I believe we must inform pa­tients, who in most cases will choose the less invasive, less risky test or procedure. Patients who are given the results of these two studies will probably not choose vertebroplasty. Informed choice matters. Patient empowerment is the best — if not the only — way to change the use of ineffective treatments short of refusing to pay for these procedures.

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Apixaban or Enoxaparin for Thromboprophylaxis

TO THE EDITOR: Lassen and colleagues (Aug. 6 issue)\textsuperscript{1} state that apixaban and enoxaparin had similar efficacy, based on the point estimate for the relative risk of all types of venous thrombo­embolism; this end point was driven mainly by asymptomatic distal deep-vein thrombosis. How­ever, according to established guidelines, non­inferiority should be shown for major venous thromboembolism (the composite of proximal deep-vein thrombosis, nonfatal pulmonary embolism, and venous thromboembolism–related death).\textsuperscript{2} The relative risk of major venous thrombo­embolism was 1.25 (95% confidence interval [CI], 0.70 to 2.23). Therefore, a relative increase in the risk of major venous thromboembolism with apixaban of 123% cannot be ruled out. This

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