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North American Spine Society
Newly Released Vertebroplasty RCTs: A Tale of Two Trials

Summary
On August 6, 2009, the *New England Journal of Medicine* published two randomized controlled trials on vertebroplasty: *A Randomized Trial of Vertebroplasty for Painful Osteoporotic Vertebral Fractures [1]* and *A Randomized Trial of Vertebroplasty for Osteoporotic Spinal Fractures [2]* . As the only multidisciplinary organization representing spine care providers, the North American Spine Society (NASS) has reviewed the studies and crafted the following comments on these important new studies and their significance to patient care.

A common initial reaction to the findings of these two prospective randomized controlled trials (PRCTs) has been surprise and even disbelief. A prominent, respected academician-surgeon who is an internationally respected leader in the field of osteoporosis research had described the procedure as "an opportunity to do something really good for patients [3]." Numerous large case series, both prospective and retrospective, had demonstrated very encouraging results with dramatic pain relief in appropriately selected patients. Even higher level data derived from a prospective comparative cohort study indicated a clear benefit over nonoperative treatment [4]. Moreover, for any physician who has performed vertebral augmentation procedures for osteoporotic compression fractures, experience has indicated that patients have dramatic pain relief, often within hours of the intervention. Some of the authors have personally seen these seemingly miraculous cases in which a bed-bound elderly person has had one or two vertebrae augmented after which they become nearly pain free and ambulatory. The evidence and experience up to the publication of the studies by Buchbinder et al. and Kallmes et al. have been overwhelmingly positive. Spine care providers are now, however, faced with a large chasm between these previous data and experiences and the latest, highest quality data.

The two PRCTs in question could be scrutinized. Like any attempt at comparing two treatments in a systematic and controlled manner, there are inevitably biases and factors that can favor one treatment over another. However, there is no such thing as an infallible PRCT. That being said, any group who undertakes such a task should be praised.

The intent of this analysis is not to in any way defame the studies or question the integrity of the authors. Instead, it is to perhaps help explore why there is such a seeming disconnect between the conclusions of these two PRCTs and previous experience and data. Without being overly critical and judgmental, there are a number of key factors that should be noticed.

Patient Selection

Fracture Acuity

The acuity of osteoporotic vertebral compression fractures (VCFs) has long been thought to influence the results of cement augmentation. Using a bone scan as a measure of fracture acuity, one study, of which Dr. Kallmes was a coauthor, concluded that "increased activity … is highly predictive of positive clinical response to percutaneous vertebroplasty [5]." While bone scans are no longer commonly used in the diagnostic evaluation of vertebral compression fractures, magnetic resonance imaging (MRI) scans are. Extrapolating from the scintigraphic data, it is generally believed that fracture edema, defined as increased signal on a fat-suppressed image or decreased signal on a T1-weighted image, noted on an MRI would be similarly predictive of a positive response to vertebral augmentation.

In fact, Buchbinder et al. utilized fracture edema or a fracture line detected on an MRI as part of the inclusion criteria. Buchbinder et al. further validated that "bone marrow edema indicates an acute fracture." However, by their description, a detectable fracture line sufficed for inclusion in the study. It is possible that the presence of a fracture line might indicate a cleft of nonunited bone, but it is unclear if this is a sign of an acute fracture. In contrast, Kallmes et al. utilized MRI or bone scan only in cases in which the fracture age was uncertain.

Both groups indicated that eligible patients had to have a fracture that was less than one year old. However, a fracture age of one year or less is not generally described as acute. In fact, most would define a maximum age of four to six weeks as the definition of an acute fracture [6, 7]. Thus, there appears to be some inconsistency between previous literature and the current studies in the description of a fracture as acute. Furthermore, it would seem that chronological age of the fracture is difficult to measure by radiographic means and would be more aptly "measured" by patient history (i.e., time elapsed since the pain started).

It should be noted that many of the patients in both the Buchbinder et al. and the Kallmes et al. studies had fractures that were less than six weeks old. In the former, 32 percent were less than six weeks old. In the latter study, 44 percent of fractures were one to fourteen weeks old. Admittedly, subgroup calculations did not demonstrate statistically significant differences between older and younger fractures with the available numbers.

Regarding fracture acuity, it is useful to consider a recently published, non-industry sponsored, non-randomized prospective double-cohort study that compared vertebroplasty to nonoperative treatment for VCFs [4]. While this study found statistically significant differences at three months follow-up, there was no difference at six months and one year follow-up. This study provides compelling evidence that pain from osteoporotic VCFs substantially diminishes over time. Furthermore, it would be reasonable to conclude that sometime between three months and six months fracture pain reduces to a level equivalent to the pain reduction that might be observed with vertebroplasty. Thus, the results of the Kallmes et al. and Buchbinder et al. studies are not surprising at all. The plurality of fractures was greater than three months old suggesting that fracture pain should have been substantially reduced. It is possible that this group was self-selecting as they may have been the most willing to be randomized to a so-called sham procedure.

Enrollment

Enrolling patients in a PRCT is a difficult task. Trying to explain to someone who is in excruciating pain that he or she will be assigned, at random, to either the group getting the new, promising procedure or to the group getting a sham injection is a difficult task. By the very nature of this conversation, many patients will not consent to the study, representing a selection bias. It is reasonable to think that patients in severe pain would more often opt to decline the study and proceed with vertebroplasty. It would have been useful to see the outcomes of this group of patients; similar to that published by Weinstein et al. in the recently published Spine Patient Outcomes Research Trial (SPORT) studies for lumbar degenerative disorders [8].

This pattern seemed to have been the case with the two studies in question. In the Kallmes et al. study, 1812 patients were initially screened, yet only 131 were entered into the study. The most common reason for not being entered into the study was patient refusal. Similarly, Buchbinder et al. required 4.5 years to accrue 78 patients at four high volume centers, reporting that 141 who satisfied all inclusion criteria declined randomization. The pain severity and functional compromise of the groups of patient who refused participation were not reported. Thus, there exists an unquantifiable selection bias in the final patient group.

Control Group

The control groups in both of these studies underwent supposed sham procedures. However, this was not so much a sham procedure as it was an alternative intervention. Injection of anesthetic into the facet capsule and/or periosteum may have had a plausible mechanism of pain relief in this patient population, albeit not fracture pain relief. While it is stated in both studies that patients had back pain, it is unclear if the origin of the back pain was the osteoporotic VCF or other common reasons for back pain in the elderly, such as arthritis facet pain. By nature of the patient population studied, “sham” facet injections may have led to decreased facet pain. Perhaps a sham procedure in which a dry needle was inserted might have been a more appropriate control.

Outcomes

In the Kallmes et al. study, the investigators stated that back pain was measured. However, there did not appear to be an effort to determine if reported back pain indeed originated from the osteoporotic fracture site. In the experience of some spine care providers, related to vertebral augmentation, it has been found useful to percuss or palpate the spinous processes systematically in order to find a level of maximal tenderness. This can then be marked with a radiographic marker to help localize the region of pain to a specific fractured vertebra. It is not uncommon for a patient to have pain that is distant from the fracture site, which would greatly diminish confidence that the perceived pain was originating from the fracture site. A bit more confusing was the assessment of “overall pain” in the Buchbinder study. It is unclear if this was an assessment of back pain or a more general measure of patients’ bodily pain.

Another important observation concerns the pain reduction observed in these two PRCTs. In the Kallmes et al. study, the authors reported an average reduction of three Visual Analog Scale (VAS) points at one month follow-up. In the Buchbinder et al. study, an average reduction of 2.3 was reported. In a recently published, industry-sponsored, PRCT comparing kyphoplasty (a comparable vertebral augmentation procedure to vertebroplasty) to nonoperative treatment, an average pain reduction of 3.5 VAS points was

reported [1]. The results of these three PRCTs do not appear to be dissimilar, notwithstanding other differences in the study.

A Look to the Future

Both groups of authors should be congratulated for undertaking the onerous task of performing high-level studies on an imminently important clinical disorder in our aging population. It is hoped that these data will help better define the indications for this potentially beneficial procedure. In addition, future PRCTs might benefit from a more strict mechanism by which patients with truly acute pain relatable to an osteoporotic VCF are enrolled. As both the Buchbinder et al. and Kallmes et al. study have taught us, this is likely to be a difficult task that may take a long period of time.

Conclusion

Beyond the lay press releases which claim "Vertebroplasty found to be useless for osteoporotic fracture and disc pain," [9] it is time for cooler heads to prevail. The medical literature thirsts for evidence. The data from these two studies must be considered carefully and thoughtfully. As discussed above, the findings of these investigations are not surprising and indeed not that dissimilar to previous data. The conclusions drawn by the authors, however, may not be as decisive as they appear. More practical conclusions should be made based on a thorough and systematic review of *all* the literature in order to better define the subgroup of patients for which vertebroplasty might be most appropriate.

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Disclosures:

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Current
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Speaking and/or Teaching Arrangements: Depuy Spine (Level C); Stryker Spine (Level B)
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Research Support: Staff and/or materials: Archus Orthopedics (Level B); Synthes Spine (Level D)
Grants: Stryker Spine (Level D)
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Research Support: Investigator Salary: Department of Defense (Level E)
Grants: Department of Defense (Level I, not directly related to the spine)

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Others: Blackstone Medical Inc. (Financial, Clinical Events Committee for clinical trial)

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Level D. $25,001 to $50,000

Level E. $50,001 to $100,000

Level F. $100,001 to $500,000

Level G. $500,001 to $1M

Level H. $1,000,001 to $2.5M

Level I. Greater than $2.5M

1. 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(6):557-568.
2. 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(6): 569-79.
3. Einhorn TA. *Vertebroplasty: an opportunity to do something really good for patients. Spine*. 2000. 25(9): 1051-1052.
4. Alvarez L, Alcaraz M, Pérez-Higueras A, Granizo JJ, de Miguel I, Rossi RE, et al.. *Percutaneous vertebroplasty: functional improvement in patients with osteoporotic compression fractures. Spine*. 2006. 31(10): 1113-8.
5. Maynard AS, Jensen ME, Schweickert PA, Marx WF, Short JG, Kallmes DF. *Value of bone scan imaging in predicting pain relief from percutaneous vertebroplasty in osteoporotic vertebral fractures. ANJR Am J Neuroradiol*. 2000. 21(10): 1807-12.
6. Ross PD, Ettinger B, Davis JW, Melton LJ 3rd, Wasnich RD. *Evaluation of adverse health outcomes associated with vertebral fractures. Osteoporosis Int*. 1991. 1(3): 134-140.
7. Gray DT, Hollingworth W, Onwudiwe N, Deyo RA, Jarvik JG. *Thoracic and lumbar vertebroplasties performed in US Medicare enrollees 2001-2005. JAMA*. 2007. 298(15): 1760-1762.
8. Weinstein JN, Lurie JD, Tosteson TD, Skinner JS, Hanscom B, Tosteson AN, et al. *Surgical vs. nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT) observational cohort. JAMA*. 2006. Nov 22;296(20):2451-2459.
9. http://www.beforeyoutakethatpill.com/index.php/2009/08/06/vertebroplasty-found-to-be-useless-for-osteoporotic-fracture-and-disk-pain/comment-page-1/.