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Consternation and questions about two vertebroplasty trials

Confronted with the unexpected results of two trials of vertebroplasty,[1,2] physicians are feeling some consternation, We had thought that percutaneous vertebroplasty helps patients with osteoporosis who sustain a painful vertebral insufficiency fracture. However, the trials found it to be no better than a sham procedure in terms of relieving pain.

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Should we abandon this popular procedure? Or are there other considerations?

How will these findings affect our practice? Should we abandon this popular procedure? Or are there other considerations that may mitigate these negative findings? And what should we tell our patients?

700,000 FRACTURES PER YEAR

Vertebral insufficiency fractures are the most common type of fracture in patients with osteoporosis. Every year in the United States, about 700,000 of them occur.

Nearly two-thirds are asymptomatic. The other one-third typically present with the acute onset of localized pain.

Vertebral insufficiency fractures often lead to chronic pain, impair the ability to walk and to perform daily activities, and accentuate thoracic kyphosis, which in turn can lead to pulmonary restrictive disease, and they raise the risk of death. Also, a patient who has a vertebral insufficiency fracture has a 20% risk of sustaining a new one within 1 year.[3]

Whether symptomatic or asymptomatic, finding a vertebral insufficiency fracture should prompt one to consider drug therapy for osteoporosis. In addition, until now, a patient who presented with the acute onset of back pain and whose evaluation revealed a vertebral insufficiency fracture would also be considered for a vertebral augmentation procedure, either vertebroplasty or kyphoplasty, to relieve the pain.

Vertebroplasty involves injecting polymethylmethacrylate cement percutaneously into the affected vertebral body. Kyphoplasty, a similar procedure, uses a balloon to create a cavity in the fractured vertebral body. After the balloon is withdrawn, the cavity is filled with cement.

TWO RANDOMIZED TRIALS OF SHAM VS REAL VERTEBROPLASTY

Two teams, Kallmes et al[2] and Buchbinder et al,[1] independently performed randomized controlled trials to see if vertebroplasty really relieves pain as well as has been reported in open studies, case series, and nonrandomized trials.[4–7]

In both trials, patients were randomized to undergo either sham vertebroplasty or real vertebroplasty. The sham procedure closely approximated the real procedure, including inserting a needle, infiltrating a local anesthetic, bupivacaine (Marcaine), into the periosteum of the posterior lamina[1] or the pedicle of the target vertebrae,[2] and opening a vial of polymethylmethacrylate so that the patient would smell the product.

Inclusion criteria

Patients in both trials had to have evidence of a recent (acute) or nonhealed vertebral insufficiency fracture.

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Pain was the primary outcome measured

In both trials, the investigators assessed the patients' pain at baseline and again at several specified intervals, using validated tools.

Kallmes et al assessed pain intensity and functional measures at 1 month (the primary outcome measured), and also at 3, 14, and 90 days and at 1 year.

Buchbinder et al assessed pain at 1 week and at 1, 3, and 6 months. The primary outcome measured was pain at 3 months. Secondary outcomes included quality-of-life measures, pain at rest, and pain at night.

Surprising results

In both trials, the mean pain scores were better than at baseline at all time points after the procedure in both the real-procedure and the sham-procedure groups. Moreover, the effect did not differ between the two treatment groups in either study.

QUESTIONS COMPLICATE THE ISSUE

These two trials should make us consider whether this intervention is warranted. We should, however, also consider some limitations of these studies that raise questions about how the conclusions should or should not alter practice.

Does local anesthetic continue to relieve pain?

In both the sham and the real procedure, the bupivacaine injection may have helped relieve pain to some extent afterward, as its anesthetic effect may last longer than we would expect from its 3-hour half-life. The effect could certainly have contributed to improvements in pain levels at the earlier time points after the procedure.

Was there selection bias?

Both studies were highly rigorous and were done at hospitals that had extensive experience with vertebroplasty. However, they may have harbored selection bias, as many more patients were screened than were randomized.

Buchbinder et al[1] screened 468 patients. Of these, 30% declined to participate, and another 53% did not meet the eligibility criteria. In the end, only 78 patients were randomized.

Kallmes et al[2] screened 1,813 patients, 300 of whom declined and 1,382 of whom were excluded, leaving 131 patients to be randomized. The reasons for exclusion were not specifically reported in many cases.

In both studies, it would be interesting to know how many of those who declined proceeded to undergo a vertebral augmentation procedure.

Did the trials have enough power?

In the study by Kallmes et al,[2] recruitment got off to a slow start. Thus, after three patients were recruited, the inclusion requirements were liberalized. The study was originally designed to include 250 patients, which would have given it a power of greater than 80% to detect differences in primary and secondary outcomes. The design was revised to include 130 patients. The statistical power was still 80%, but this was to detect a greater difference in the outcomes than originally projected.

Had the window of opportunity already closed?

Vertebroplasty may have a window of opportunity within which it is most effective. Sooner is probably better than later, but it would be good to identify this time frame.

The highest priority after a fracture is to treat the osteoporosis

Kaufmann et al[9] reported that patients with older fractures needed slightly more analgesic drugs after the procedure. It has been shown previously that patients who are the most likely to respond to a vertebral augmentation procedure are those with fractures that occurred between 1 and 12 months prior to the procedure and who have evidence that the fracture was recent, ie, edema on magnetic resonance imaging (MRI) or increased uptake on a bone scan.[10]

Other studies suggested that intervention works best in patients who have had uncontrolled pain lasting less than 6 weeks.[8,11] (In the study by Buchbinder et al,[1] only 32% of the patients in either group reported pain lasting less than 6 weeks.)

The study by Kallmes et al included patients whose pain had begun within 1 year previously. However, if the duration of pain (ie, the age of the fracture) was uncertain,

MRI was done to look for edema, which would indicate the fracture was fresh. It is thus unclear whether all patients in this study truly had an acute or subacute fracture, since all did not undergo confirmatory MRI.

Why did so many patients cross over from sham to real treatment?

Patients in the Kallmes trial[2] could cross over from one treatment group to the other as early as 1 month after the procedure. And, in fact, 43% of patients in the sham-treatment group did choose to cross over by 3 months. In contrast, after real vertebroplasty, significantly fewer—only 12% ($P < .001$)—crossed over to receive the sham procedure. The patients who crossed over from the sham-procedure group to receive vertebroplasty experienced an early improvement in pain, but this was not sustained at 1 or 3 months of follow-up.

The higher crossover rate in the sham-procedure group suggests they were dissatisfied with this intervention, although their outcomes were not significantly better after they got the real procedure. The patients who first received the sham treatment and elected to cross over to vertebroplasty had higher pain and disability scores at baseline. Thus, they may have had other, more chronic causes of pain or other factors affecting the likelihood of a response, particularly of a durable or sustained response.

Many more patients were screened than were randomized

How do the interventions compare with medical therapy?

Earlier studies showed that vertebroplasty relieves pain almost immediately.[4–6] But the benefit does not last: at 6 weeks and up to 12 months later there is no difference in either pain or functional capacity reported in patients receiving vertebroplasty vs conservative treatment.[4,6,7] It would thus appear that pain gradually diminishes over time after a vertebral insufficiency fracture, as the fracture heals.

The recent studies[1,2] raise the possibility that the pain relief is due to the local anesthetic, not the vertebroplasty itself. We do not know, however, if either vertebroplasty or the sham procedure is superior to conservative medical management. Prospective multicenter trials are under way to address this question.[11]

Further complicating the issue, the two trials did not keep track of medical treatments patients were receiving concomitantly during the trial period. It is thus more difficult to compare the pain assessment outcomes following invasive procedures—real or sham.

Would kyphoplasty be better?

These studies addressed one procedure, vertebroplasty, and the results and conclusions should not be generalized to kyphoplasty. A prospective randomized trial of kyphoplasty is clearly warranted.

If kyphoplasty is found to be better than a sham procedure, then vertebroplasty should be re-examined in comparison with kyphoplasty. In any future studies, it will be important to select patients rigorously (eg, to include only patients with recent fractures), to match patients according to concomitant therapies, and to consider other potential superimposed causes of back pain in this elderly population, which has a high prevalence of back pain.

HOW SHOULD MY PRACTICE CHANGE? WHAT SHOULD I TELL PATIENTS?

Having considered the results, conclusions, and limitations of these two randomized trials, particularly in terms of recruitment, I cannot say that my practice has changed in terms of referring patients who have a vertebral compression fracture to an interventionalist. However, the education that I provide to patients has changed.

In my mind, the highest priority for a patient with a vertebral insufficiency fracture is to treat (or to reassess the current treatment of) the underlying systemic disease, ie, osteoporosis. This is especially true since most vertebral insufficiency fractures are asymptomatic.

On the other hand, a patient with a painful vertebral compression fracture needs prompt attention and consideration for interventional pain relief. Rapid pain relief is desirable. And in uncontrolled trials,[4–7] vertebroplasty and kyphoplasty rapidly relieved vertebral pain. However, it may be that an anesthetic injection is equivalent to vertebroplasty and could accomplish the goal of immediate pain relief just as well.

The pain relief from sham or real vertebroplasty may not be durable, and 3 to 12 months later the pain benefit may be no greater than if more conservative therapy had been pursued.

It is essential to determine the most appropriate window for treatment as well as the most appropriate candidates on whom to perform a procedure. The recently published studies[1,2] may have had significant patient selection bias and may not have optimized the window of opportunity for vertebral augmentation performance. There were many patients who declined the study, and some were excluded because of acute pain requiring hospitalization.

As a rheumatologist treating patients with osteoporosis, it is my responsibility to discuss with the patient and family the potential treatments available, to discuss the associated possible risks and benefits, to report on available evidence, and to refer patients to an appropriate interventional specialist if they desire. In light of the lack of superior pain reduction with vertebroplasty than with a sham procedure, many patients may opt for conservative therapy.

I cannot say my practice has changed, but what I tell patients has

It is thus appropriate to determine the acuity of the fracture and to have a frank discussion with the patient about the options for pain management. Opiate drugs pose risks in elderly patients, particularly altered mentation, somnolence, interference with balance, and risk of falls. Vertebroplasty or anesthetic injection may rapidly relieve the pain and reduce the need for opiate therapy. Not yet subjected to the rigors of a randomized placebo-controlled trial, kyphoplasty may yet prove to be better than a sham intervention.

It is essential to determine if there is a role for vertebral augmentation in a select patient population—perhaps selected on the basis of the time that has elapsed since the fracture occurred (determined objectively), the severity of the fracture, and other factors. Perhaps a subset of patients would gain greater benefit from the procedure, whether it amounts solely to acute pain reduction or perhaps to a more durable response.

The recent studies by Kallmes et al[2] and Buchbinder et al[1] found vertebroplasty and sham vertebroplasty to be equally effective in reducing pain and improving function. However, given the limitations of each of these studies, particularly the low numbers of patients, it is difficult to establish that vertebral augmentation procedures should no longer be done. And vertebroplasty may still benefit correctly selected patients. ■

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