Vertebroplasty 'Benefits' May Be Placebo Effect

BY SHERRY BOSCHERT

EXPERT ANALYSIS FROM A MEETING ON OSTEOPOROSIS

SAN FRANCISCO – Vertebroplasty worked no better than sham surgery to reduce pain and disability from vertebral fracture, according to data from recent randomized, controlled trials that put nonsurgical therapies firmly in the first line of treatment.

Osteoporotic vertebral fractures should be treated aggressively with antiresorptive or anabolic therapy for at least 6-12 weeks before considering surgery, Dr. Douglas C. Bauer said at a meeting on osteoporosis sponsored by the University of California, San Francisco. Optimize medical therapy, physical therapy, and other options that might be appropriate such as adding calcitonin or referring the patient for a facet joint injection, he said.

Even after all that, clinicians should consider kyphoplasty before resorting to vertebroplasty, said Dr. Bauer, who is professor of medicine and of epidemiology and biostatistics at the university.

Findings from one unblinded, randomized trial suggest that kyphoplasty may reduce pain and disability, compared with conservative care initially, though the difference in results is less apparent 1 year after surgery.

Despite data from numerous uncontrolled studies suggesting that vertebroplasty also lessens pain and improves function, findings from two well-designed controlled trials "raised a brouhaha" and surprised investigators by showing vertebroplasty to have no benefit, "suggesting that a very commonly done procedure is not helpful," he said. It's unclear whether the uncontrolled trial results were due to an extended placebo effect or some other factor.

In kyphoplasty, surgeons insert a balloon device to reduce the cervical fracture, remove the balloon, and replace it with cement. Vertebroplasty injects cement only, without the balloon, and does not attempt to increase vertebral height. Both are minimally invasive surgeries that usually are performed under general anesthesia but can be done using local anesthesia, often with conscious sedation.

The unblinded trial of kyphoplasty randomized 149 patients to kyphoplasty and 151 to usual nonsurgical care. "The patients were typical of who we see with vertebral fracture," Dr. Bauer noted.

The primary results showed that 1 month after surgery, scores on the Short Form-36 (SF-36) Physical Component Summary had increased from 26 at baseline in both groups to 27 in the kyphoplasty group and 33 in the control group, a significant difference between groups (Lancet 2009;373:1016-24).

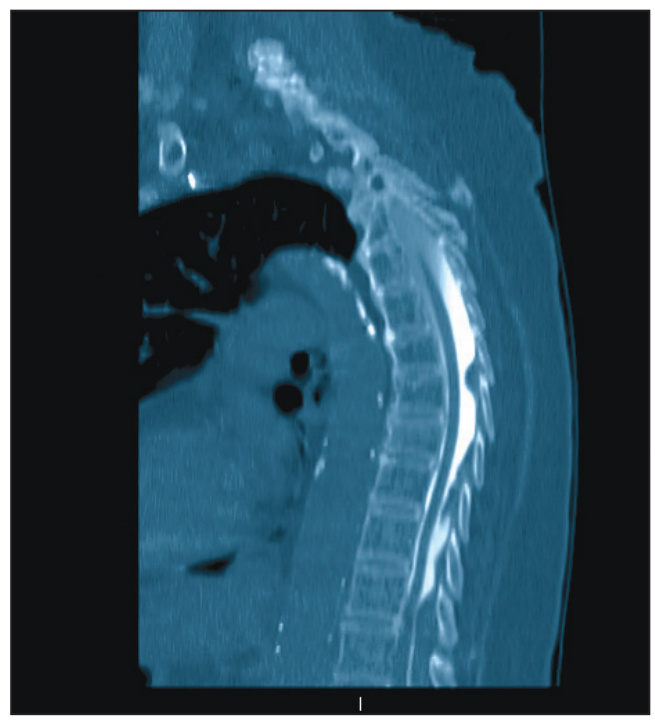
Follow-up continued out to 3, 6, and 12 months after surgery, and results were significantly better in the kyphoplasty group at all time points for the SF-36 Physical Component, patient-reported Visual Analog Scale (VAS) scores for back pain, and the number of days of limited activity in the previous 2 weeks.

Although statistically significant, some of the differences between groups were more clinically significant than others. The self-reported VAS pain scores, for example, differed between groups by only 1 point on a 10-point scale at 12 months. The kyphoplasty group, however, enjoyed an average of 60 fewer days of limited activity during those 12 months, compared with the control group, which "patients may be most interested in," Dr. Bauer said.

At 24 months, only the difference in pain scores remained statistically significant between groups (J. Bone Miner. Res. 2011;26:1627-37).

More trials of kyphoplasty are needed before the surgery becomes widespread, Dr. Bauer said.

A separate uncontrolled trial that randomized 202 patients to vertebroplasty or usual care similarly found statistically greater improvements in the vertebroplasty group in VAS pain scores at 1 month (a decrease of 5 points) and 1 year (a 6-point drop), compared with usual care (a 3- and 4-point drop, respectively). Patients in the surgery arm also reported less narcotic use (Lancet 2010;376:1085-92).



COURTESY DR. VICTOR JARAMILLO/DR. ARAVIND POTHINENI

Clinicians should consider kyphoplasty before resorting to vertebroplasty for an osteoporotic fracture (above).

The two well-designed controlled trials of vertebroplasty contradict other findings, however. Patients were taken to the operating room before randomization. The members of the control group received sham surgery that included needle insertions in their backs and the breaking of a vial of chemicals to disperse a chemical smell. Outcomes assessors were blinded to randomization.

In one study of 71 patients, scores for back pain decreased significantly in both the real and sham surgery groups, but outcomes did not differ significantly between the groups at any time point out to 6 months (N. Engl. J. Med. 2009;361:557-68).

In the other study of 131 patients, both groups showed immediate improvements in disability and pain scores but no outcomes differed significantly between groups at 1 month (N. Engl. J. Med. 2009;361:569-79).

While it's conceivable that the benefits reported for vertebroplasty and kyphoplasty in uncontrolled studies are due to an extended placebo effect, the likelihood that the placebo effect would last for as much as 24 months of follow-up is unclear, Dr. Bauer said.

Some have suggested that the sham-surgery studies included a harder-to-treat population by accepting patients with vertebral fractures up to 1 year in duration, but a subsequent analysis of data limited to fractures of less than 6 weeks duration found no change in the overall results.

Case series have shown that anesthetic or steroid injections alone can reduce vertebral fracture pain, which may explain the improvement in pain scores in both the real and sham-surgery groups in the vertebroplasty trials, he suggested.

There also may be a difference between the two surgeries that produce different results from kyphoplasty or vertebroplasty. Randomized, controlled trials comparing the two are underway.

Further research is needed on optimal patient selection, on whether the surgeries prevent kyphosis, and on long-term outcomes, Dr. Bauer said.

The 700,000 vertebral compression fractures in the United States each year hospitalize more than 150,000 people.

Dr. Bauer has received research funding from Amgen and Novartis. ■

MD Encouragement Improves Antiresorptive Tx Adherence

BY SHERRY BOSCHERT

EXPERT ANALYSIS FROM A MEETING ON OSTEOPOROSIS SPONSORED BY THE UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

SAN FRANCISCO – Talking to patients after they start an antiresorptive drug for osteoporosis is better than laboratory testing to convince them to stay on therapy, according to Dr. Douglas C. Bauer.

Bone mineral density testing determines the need for antiresorptive medication, but it's less helpful in monitoring the effects of treatment or adherence to therapy than is talking to patients. A test showing bone loss in the first year of treatment can confuse patients and doesn't necessarily mean they are not responding to treatment, said Dr. Bauer, professor of medicine and of epidemiology and biostatistics at the university.

Besides, most of the patients who stop osteoporosis therapy within 3 years do so within the first few months of treatment, so annual bone density testing is unlikely to improve adherence, he added.

Biochemical markers of bone turnover eventually may become the standard for monitoring treatment, "but we're not there yet," he said at the meeting.

Studies have shown that follow-up discussions after a patient starts antiresorptive medication is the factor that improves adherence, not measuring bone density or bone turnover markers.

Most of the patients who stop osteoporosis therapy within 3 years do so within the first few months of treatment, so annual testing of their bone mineral density is unlikely to improve adherence.

Dr. Bauer said he tells patients not to expect routine follow-up bone density testing and asks about and encourages adherence at every patient visit. If a patient develops a fracture while on therapy or is considering a drug holiday after 5 years on alendronate, he then considers ordering follow-up bone mineral density testing.

"There's a caveat: This may not be the right algorithm for tertiary care centers with severe or complex patients," said Dr. Bauer.

Although bone mineral density measurements are very precise, small differences in position or "noise" in the measures can produce apparent changes that are not clinically meaningful. To assess whether a change in bone density is "real," he recommended a useful equation called the "least significant change" equation: Multiply the coefficient of variations by three; if the sum is less than 4.5%, then the change may be due to chance.

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For example, if the coefficient of variations in hip bone density is 1.5%, the least significant change is 4.5%. If a patient lost 3% in bone density, there is approximately a 10% chance that there was no change in bone density, he said.

"A somewhat more fundamental question is not just whether the measurements [are] real, but are they meaningful?" Dr. Bauer said.

Analyses of data from the Fracture Intervention Trial (FIT) show that patients on alendronate who lost up to 4% in total hip bone density in the 1-2 years of treatment still had 53% fewer vertebral fractures compared with their counterparts on placebo who lost similar amounts of bone density. Patients who lost up to 4% in spine density had 60% fewer vertebral fractures compared with their counterparts on placebo (Osteoporos. Int. 2005;16:842-8).

Biochemical marker measurements could identify nonadherence, but 'it's cheaper just to ask.'

DR. BAUER

Then there's the "regression to the mean" argument that patients who have an unusual response in the first year of antiresorptive therapy will develop a more typical response if treatment is continued, he said. A separate analysis of FIT data showed that 92% of patients who lost up to 4% of hip bone density in the first year of therapy gained an average of nearly 5% in bone density in the second year of treatment (JAMA 2000;283:1318-21).

A more recent analysis of annual bone mineral density data in FIT showed that variation in the change in bone density over a 3-year period was mainly measurement-related, within-person variation. Treatment-related, between-person variation played a much smaller role (BMJ 2009;338:b2266).

That helps explain how patients can "lose" bone density but still have fewer fractures, Dr. Bauer said at the meeting. "It's reassuring that 98% on alendronate

gained more than 0.02 g/cm^2" in FIT.

Antiresorptive therapy decreases biochemical markers of bone turnover, but there is a lot of biologic variability and no clear threshold for efficacy. Biochemical marker measurements could be used to identify nonadherence to treatment, but "it's cheaper just to ask," he said.

In a study of 2,382 osteoporotic women starting a year of risedronate therapy, the women were randomized to get bone turnover markers measured at weeks 13 and 25 or to routine visits without marker measurements.

The results showed no difference in adherence rates between the groups (J. Clin. Endocrinol. Metab. 2007;92:1296-304). In the marker measurement group, the adherence rate was 225% worse than in the control group if the marker results suggested a "bad" response to therapy (less than a 30% decrease in marker levels).

"That was unexpected," Dr. Bauer said. "Bone turnover markers by themselves are not helpful for increasing adherence" to therapy.

A separate randomized study of 75 women starting raloxifene treatment for low bone density randomized them to no monitoring; nurse visits at months 3, 6, and 9; or nurse visits plus bone turnover marker measurements. The nurse visits improved adherence to therapy compared with no monitoring, but biomarker measurements did not add anything to the nurse visits (J. Clin. Endocrinol. Metab. 2004;89:1117-23).

In general, approximately 30%-40% of patients stop taking antiresorptive drugs within 1 year, he said.

Dr. Bauer said he has received research funding from Amgen, Novartis, and Procter & Gamble. ■