Alendronate and fusion

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Spinal lumbar fusion surgery has become a relatively common surgical procedure, and bone grafting is frequently performed during the surgery. The rate of lumbar spine fusion surgery for patients over the age 60 in the US is rapidly increasing. It is patients in this group who are more likely to have a diagnosis of osteoporosis, which is becoming an increasing burden on public health. Bisphosphonates, such as alendronate, are widely used as a treatment for osteoporotic patients. Bisphosphonates are classified as antacatabolic drugs and are used to treat bone conditions that are a result of catabolism such as stress-shielding or disuse osteoporosis. Alendronate acts by inhibition of osteoclasts and thereby affects bone remodeling. The effect that bisphosphonates have on bony healing in patients undergoing spinal fusion surgery has been little studied until now.

In their study reported in this issue of the Journal of Neurosurgery: Spine, Nagahama et al. investigated this effect in 40 patients undergoing single-level posterior lumbar interbody fusion who had been diagnosed with osteoporosis; the authors randomly allocated the patients to an alendronate group or a control group given low-dose vitamin D supplementation. In this prospective controlled randomized trial, the effect of alendronate on fusion was studied based on a combination of radiographic, clinical, and biological parameters. Of the total of 40 patients enrolled into the study, 4 were lost to follow-up leaving a total of 36 patients who were followed up for 1 year postoperatively. The surgical technique involved pedicle screw instrumentation and discectomy followed by local bone graft harvesting that was subsequently mixed with tricalcium phosphate and packed into carbon polyetheretherketone cages before being positioned in the interbody space. Radiographic assessment involved functional radiography, including standing flexion-extension radiographs and CT scans. Clinical assessment was made using the Oswestry Disability Index. Laboratory assessments of bone turnover were made using serum bone alkaline phosphatase and markers of bone resorption through the measurement of serum and urine Type I collagen cross-linked N-telopeptides. Data were collected preoperatively and at 3, 6, 9, and 12 months postoperatively.

The authors demonstrated a significantly higher fusion rate in the alendronate group (95%) than in the control group (65%). The significantly higher fusion rate in the alendronate group is a surprising finding given the result of previous research showing a decreased chance of solid fusion with the administration of alendronate. Furthermore, the fusion rate in the control group was very low. The reasons for this unusually low rate may be multifactorial, and may entail the inclusion of only patients with osteoporosis and relatively strict radiographic criteria being employed to assess fusion. In addition, cage subsidence was more frequently encountered in the control group as were subsequent (postoperative) vertebral compression fractures, although neither of these findings achieved statistical significance. Clinical outcome measures also showed a trend toward better clinical results in the alendronate group, but the difference again was not significant. A key message of the study was to demonstrate that the biological process of spinal fusion is modulated by alendronate. Of note, the biochemical analysis of bone turnover suggested that alendronate had an inhibitory effect both in the early phase of fusion with reduced bone resorption and later, with less bone formation at 6 months postoperatively. The authors also argue that alendronate brings certain mechanical advantages that outweigh its biological disadvantages.

The study has a number of difficulties and limitations. For instance, the control group received vitamin D instead of placebo or nothing. There is no indication that the alendronate group also received vitamin D. The authors excluded any patients who were older than 85 years or had previously diagnosed and treated osteoporosis. The study patients therefore all had newly diagnosed osteoporosis, which would have posed an ethical conflict for the research team had they not treated some of these patients—hence the use of vitamin D in the control arm. There is no doubt, however, that the use of vitamin D in the control arm could represent a confounding factor.

A further limitation was the relatively small number of patients recruited, which unfortunately meant that the study was statistically underpowered for subgroup analyses. Nevertheless, the difference in fusion between groups is such that a further study with larger numbers of patients is an enticing prospect, particularly in light of the trends seen in subsidence and compression fractures that did not reach significance levels.

The methods used to assess fusion were relatively strict, with the inclusion of both CT and functional ra-
diography, yet there is no ideal standard to assess fusion. The difficulties of assessing bony fusion and in particular its overestimation based on CT parameters have been previously highlighted in histological studies. Furthermore, previous research has questioned whether CT provides new useful information if plain radiographs show good evidence of fusion or pseudarthrosis, although CT has been shown to be superior to plain radiography when assessing bridging trabeculation through an interbody cage. It is also entirely possible that premineralized osteoid may be functionally fused but appear radiolucent on radiographic film. This demonstrates the disadvantage of using imaging modalities in determining fusion rates. In studies using animal fusion models, investigators are able to assess fusion based on manual palpation once the animals are killed, and this is a robust method of assessing fusion. In their study, Nagahama et al. employed functional radiography, which has limitations due to the effect of the pedicle screws and rod constructs eliminating movement. In addition, the patients were followed up for 1 year, and it is possible that the fusion rate in the control arm may have increased up to 2 years postoperatively.

The results of previous research using animal models both in vivo and in vitro suggest that alendronate has an inhibitory effect on fusion. Other animal studies suggest that alendronate decreases fusion mass remodeling without inhibiting fusion rate. The effects of alendronate on osteoclast and osteoblast function appear to be dose dependent.

Nagahama et al. have attempted to answer an interesting question regarding the effects of alendronate on healing in osteoporotic bone. The ideal length of time that alendronate should be administered postoperatively in osteoporotic patients undergoing fusion surgery and whether starting early and stopping after 3 months is better than starting at 3 months and continuing with treatment are unknown. Work conducted by Takahata et al. in an ovariectomized rat model suggests that administration of bisphosphonates should be delayed during the immediate postoperative period. Other findings suggest that short-term low-dose alendronate treatment does not impair bone formation but increases bone ingrowth in the interbody cage in a porcine model.

In summary, Nagahama and colleagues should be congratulated for producing some interesting information regarding the effect of alendronate on spinal fusion. This work is particularly relevant as increasing numbers of osteoporotic elderly patients already receiving alendronate are undergoing spinal fusion surgery. Future research in this area should probably include a larger number of patients with a placebo control arm studied over a longer duration. The effect of vitamin D supplements on fusion may be significant and should be investigated.

References


Response

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We would like to thank Drs. Fehlings and Mobasher for their constructive comments on our study. As high-
lighted in their editorial, there were several limitations in this study. We observed significant differences in the radiographic fusion rates and occurrence of subsequent vertebral fractures between the 2 groups, but the differences in cage subsidence and clinical outcome (Oswestry Disability Index score) did not reach the significance level. A small sample size or underpowered statistical analysis was a methodological weakness of this study. Our strict inclusion criteria—candidates for a single-level posterior lumbar interbody fusion with untreated osteoporosis and no degenerative scoliosis—helped to minimize confounding factors between the treatment groups, but they also presented challenges in recruiting patients. Although approximately 200 instrumented lumbar spine fusions are performed annually in our hospital, only 40 patients met our inclusion criteria during the 15 months of recruitment. As Resnick et al. suggested in their article, if an analysis is performed to determine the sample size necessary to ensure a power of 0.8 (or an 80% chance of detecting a significant effect) in a study in which the good outcome rate is 60% in the control group and 70% in the treatment group, approximately 355 patients would be needed in each treatment group. Considering the magnitude of these numbers, a well-designed multicenter clinical trial using standardized surgical procedures will be the only solution to achieve more statistical power.

Accuracy in radiographic assessment of fusion status is the issue to be addressed. We used strict criteria to diagnose a solid fusion by fluoroscopy and CT scans, but radiographic assessment in an instrumented spinal fusion had inherent bias in overestimating fusion status due to stability provided by spinal instrumentation. In an ultimate evaluation of fusion status, the patients must undergo removal of pedicle screw instrumentation and surgical exploration. In our previous studies employing radiography and surgical exploration, however, radiographic assessment was adequate to detect the difference in fusion rates between the 2 treatment groups. Without surgical exploration, we could not argue the “true” fusion rate, but we could successfully compare the 2 treatment groups by means of a strict radiographic assessment.

The setting of the control group was another confounding factor. For ethical reasons, the patients in the control group were given vitamin D instead of a placebo. Grant et al. conducted a large clinical trial involving 5292 osteoporosis patients to evaluate the efficacy of vitamin D and calcium in the prevention of secondary fractures, and they did not find any statistically significant difference in the incidence of secondary fractures between the participants treated with vitamin D and calcium and those assigned to the placebo arm (12.6% vs 13.4%). Porthouse et al. also carried out a randomized controlled trial involving 3314 women with osteoporosis and found no evidence that calcium and vitamin D supplementation reduces the risk of clinical fractures in women with risk factors for hip fracture. Thus, vitamin D does not have as strong evidence as bisphosphonate for prevention of osteoporosis-related fractures, but obviously does have effect on bone biology. We hope that a large multicenter clinical trial with a placebo control arm, as proposed in this editorial, will be undertaken in the future.

In the current preliminary clinical trial, we attempted to answer the key question related to osteoporosis and spinal fusion: Are bisphosphonates clinically advantageous for spinal fusion or not? Based on the findings, the bisphosphonate alendronate provided favorable mechanical circumstances overcoming its detrimental biological effect on the healing process of spinal fusion. We recommend the use of bisphosphonate medication in osteoporosis patients undergoing spinal fusion throughout the pre- and postoperative periods.

Finally, we still have several questions to be answered in future research: 1) How long should patients take bisphosphonates before and after spinal fusion surgery to improve the strength of vertebral bodies? 2) Could the current findings in a single-level posterior lumbar interbody fusion be applied to other situations including multi-level spinal fusion, or correction of spinal deformities? 3) How will different types of spinal fusion, especially posterolateral lumbar fusion, affect the fusion process under bisphosphonate treatment? 4) Does bridging bone under bisphosphonate treatment have sufficient mechanical properties and bone quality?

In response to demand from the growing number of patients with osteoporosis, basic and clinical investigations related to bisphosphonate and spinal fusion will be encouraged to answer these questions.

References

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