EDITORIAL

Bisphosphonates do not impair spinal fusion

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OSTEOPOROSIS is defined as diminished bone mineral density and bone quality resulting in increased risk of fracture. This is a chronic condition that is underappreciated and undertreated, even after the occurrence of fragility fractures.^{1,2} Osteoporosis is also very common in patients undergoing elective spine surgery, occurring in 20% or more of patients, and rates are often higher in patients undergoing revision or deformity surgery.³ Two classes of medications are used to treat osteoporosis: antiresorptive and anabolic. Antiresorptive medications include bisphosphonates, denosumab, calcitonin, and estrogens and selective estrogen receptor modulators. Bisphosphonates are the most commonly used drugs for treating osteoporosis because they are inexpensive (generic options are available), usually well tolerated, and can be given orally. However, their mechanism of action (inhibition of osteoclasts) and their theoretical negative effect on bone healing, which may follow an uncoupling of balanced osteoclastic and osteoblastic activities, has caused concern among spine surgeons that bisphosphonates will interfere with bone healing after fusion.

Bisphosphonates inhibit a key enzyme of the mevalonate pathway that reduces osteoclastic bone resorption ability and induces osteoclastic apoptosis.⁴ These mechanisms of action result in a rapid decrease in bone turnover along with increased bone mineral density and lower fracture risk. In fracture models in animals treated with bisphosphonates, bone remodeling of the callus is slowed but mechanical strength is maintained as a larger callus is formed in treated than control animals. A similar phenomenon likely occurs during spine fusion.

Although results in animal studies are conflicting with regard to whether spine fusion is affected by bisphosphonates,^{5,6} bone healing after fractures in humans, including spinal fractures, does not appear to be affected by the use of bisphosphonates either before or after fracture.^{7,8}

Bisphosphonates are analogs of pyrophosphate and

bind to hydroxyapatite crystal structures. The nitrogen-containing bisphosphonates in clinical use today have a high affinity for bone and rapidly precipitate into the bone structure, particularly when there is active remodeling such as after fracture or spinal fusion. Discontinuation of bisphosphonates results in their slow release from bone surfaces and continued local bioactivity for months and years to follow. For alendronate the mean half-life is estimated to be at least 10 years.⁴ Thus, stopping bisphosphonate treatment before surgery does not preclude the medication from having an effect on bone during the perioperative period. In this regard, the collective experience of patients who have undergone elective spine surgery contemporaneously with the use of bisphosphonates (regardless of whether this treatment was withheld perioperatively) serves as a natural experiment regarding the potential clinical impact this class of drug has on spinal fusion.

The current study by Guppy et al. presents the results of this “natural experiment” by analyzing the impact of bisphosphonate use in patients from the Kaiser Permanente integrated healthcare system who underwent elective spinal fusion surgery between 2009 and 2016.⁹ Kaiser Permanente has a long history of being a leader in osteoporosis care.¹⁰ In osteoporotic patients given antiosteoporotic medications according to the recommendations of the Kaiser Permanente Healthy Bones Program, Dell observed a 40% reduction in hip fractures.¹⁰

In the current study, the authors analyzed patient data from the Kaiser Permanente Spine Registry for 1040 patients with osteopenia or osteoporosis who underwent elective lumbar fusion surgical procedures including 93 surgeons at 17 institutions. Of these patients, 467 used bisphosphonates preoperatively. Follow-up was more than 5 years. The study goal was to determine if bisphosphonate use had an effect on rates of revision surgery for nonunion. The authors used a rigorous risk-adjusted statisti-

cal method to correct for differences at baseline and for known risk factors.

In their study, Guppy et al. found a low overall rate of surgery for nonunion (1.3%) in all patients. In osteopenic patients, no patients using bisphosphonates had surgery for nonunion, while 2.4% of patients without bisphosphonate use had surgical treatment, although the difference was not statistically significant. For osteoporotic patients, surgical treatment for nonunion occurred in 0.85% of bisphosphonate users and 1.89% of nonusers, findings that also were not statistically significantly different.

The findings of this study are consistent with the observations from a recent meta-analysis of 7 randomized trials that compared the effects of bisphosphonate to those for a placebo control in osteoporotic lumbar fusion patients.⁷ For that meta-analysis, the authors reported that statistically significant differences were found that favored bisphosphonate use for increasing the rates of fusion success while decreasing the rates of screw loosening, postoperative fracture, and cage subsidence. The standardized mean risk difference was 7% for fusion, indicating a small positive effect for bisphosphonates. Much greater effects were seen in mechanical outcomes. In bisphosphonate patients, postoperative fractures were reduced by 80%, pedicle screw loosening by 44%, and cage subsidence by 45%. This meta-analysis provided strong evidence, which was confirmed in the study by Guppy et al., that bisphosphonate use has a small positive effect or at worst no adverse effect on fusion healing. Further, the meta-analysis confirms that effective osteoporotic management reduces complications related to low bone mineral density and poor bone quality, such as fracture, screw loosening, and cage subsidence, in osteoporotic patients.

Animal studies of lumbar fusion models allow assessment of time-dependent effects of bone healing.⁵ However, the effects of bisphosphonates on fusion success in these animal models are inconsistent, with some showing a negative effect and others no effect.^{6,11} Unfortunately, this basic science work, along with the theoretical potential that uncoupling balanced osteoclastic and osteoblastic activity could adversely impact fusion, has caused some spine surgeons to be concerned about the perioperative use of this medication. Given the results of the current study by Guppy et al. and the meta-analysis by Liu et al.,⁷ the concerns of a negative effect of bisphosphonate should be tempered.

The current study's main strength is that it includes a large cohort of patients, treated by a large number of surgeons, with a definitive diagnosis of diminished bone density and known treatment with bisphosphonate. Each patient who had revision surgery for complications had prospective documentation regarding the surgical indication so that the patients with nonunions could be accurately abstracted. While this is a strength of the study, it is also a weakness, since most instances of nonunion are either undetected or left untreated, without revision surgery. This study only detected the rate of "symptomatic" nonunion treated with revision surgery, and not the overall rate of nonunion, which undoubtedly is substantially higher than the 1.3% overall rate reported by Guppy et al., especially in patients with diminished bone quality regardless of whether they are taking osteoporosis medications.¹² While

the loss to follow-up from change in insurance status is unknown, the Kaiser system is known to be less sensitive to challenges of this nature. The follow-up period in this study was long (over 5 years) and therefore most symptomatic nonunions for which surgical treatment was offered and accepted were likely counted in this study. The results generalize well to the US population as the institutions were located in a number of states (not all on the West Coast), and these institutions care for both routine and complex spinal disorders.

The study has noteworthy limitations. The timing and dosing of the bisphosphonates were not provided, nor can these data be confidently known based on the methodology used. Most specifically, there was no mention of dosages, and therefore the assumption is that there was no means to control for surgeon practices regarding perioperative use of bisphosphonates (i.e., which, if any, of the 467 patients using this drug preoperatively were instructed to modify use perioperatively). This was a simple observational study of a natural experiment; it was not a controlled clinical trial. Thus, the results of this study provide practical information but do not directly answer the question regarding whether patients who are instructed to hold compared to those instructed to continue routine perioperative use of bisphosphonates experience different rates of fusion success. Prolonged bisphosphonate use may lead to results that are different from those occurring with short-term use of 1–2 years. In addition, a variety of surgical techniques and different bone induction products were used. The effects of bisphosphonates on bone healing in humans in whom demineralized bone matrix and bone morphogenetic proteins are also used are largely unknown. Patient-reported outcomes were not reported for this study, and the occurrences of other osteoporotic complications, such as screw loosening, cage subsidence, and fracture, were not analyzed. Other causes of reoperation may have been influenced by both osteoporosis and bisphosphonate medication but were not reported.

Guppy et al. should be congratulated on utilizing a robust database to address an important question regarding the effects of bisphosphonates on spinal fusion. The finding that bisphosphonate use was not associated with adverse effects on healing is significant and should be reassuring to spine surgeons. The findings of Guppy et al. are consistent with knowledge gained from clinical trials of fracture prevention, in which bisphosphonates had only a small positive effect on bone mineral density but reduced fractures by more than 50%.¹³ The mechanism of action of bisphosphonates does not increase osteoblastic activity, and thus these drugs may have less effect on promoting bone healing (i.e. fusion) than other agents, but bisphosphonates do improve the mechanical function of bone, thus reducing complications such as subsidence and screw loosening. Collectively, the information from clinical studies evaluating the impact of bisphosphonates on spinal fusion success does not support the concerns that have been previously raised from early animal models and basic theoretical assumptions. On balance, bisphosphonates do not appear to adversely affect fusion outcomes; if anything, bisphosphonates may improve these outcomes.

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Disclosures

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