Editorial

Biologic enhancement of spinal fusion with bone morphogenetic proteins: current position based on clinical evidence and future perspective

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Spinal fusion may be indicated for spinal instability and/or deformity. Advancements in spinal fusion have significantly increased the fusion rate. However, the validated biomechanical properties of modern instrumentation cannot attain 100% fusion because induction of heterotopic bone formation requires a complex balance of biologic factors and operative techniques. Currently, iliac crest autologous bone grafting (ICBG) is the gold standard to enhance biologic spinal fusion. Autogenous bone has osteogenic, osteoinductive, and osteoconductive abilities. However, ICBG is associated with several disadvantages, including increased procedure time, limited donor-site availability, and donor-site pain, with rates that vary significantly in the literature.

One possible alternative to ICBG is bone morphogenetic proteins (BMPs)—a group of growth factors belonging to the transforming growth factor superfamily, which are known to elicit new bone formation (1). Among BMPs, recombinant human (rh)BMP-2 and rhBMP-7 are commercialized for limited indications.

rhBMP-2 was first approved by the United States Food and Drug Administration (FDA) in 2002 for use in single-level anterior lumbar interbody fusion from L4 to S1 with a proprietary titanium interbody cage. rhBMP-7 has received 2 FDA approvals through the Humanitarian Device Exemption process, and is indicated as an alternative to autograft in compromised patients. Despite this limited approval, use of BMPs in lumbar spinal fusion procedures increased sharply to 45% in 2008 (off-label use accounted for 85% of applications). However, after the 2008 FDA Public Health Notification about BMP-related complications and revelations regarding methodologic and financial problems in industry-sponsored trials, use of BMPs in lumbar spinal fusion surgery has gradually decreased to 25% (2). With regard to rhBMP-2, the Yale University Open Data Access (YODA) Project conducted 2 meta-analyses, including data from industry-sponsored trials, to evaluate its safety and effectiveness. They reported that rhBMP-2 demonstrated higher radiographic fusion rates than ICBG, though both groups showed equally significant clinical improvements (3,4). When it comes to rhBMP-7, only 3 randomized prospective studies exist. Among them, Vaccaro *et al*. compared the effectiveness of rhBMP-7 [also known as osteogenic protein-1 (OP-1)] and ICBG in noninstrumented posterolateral fusion for spondylolisthesis at 3 years postoperatively, and concluded that OP-1 putty was statistically equivalent to autograft with respect to both radiographic and clinical outcomes (5). However, one limitation of their study was lack of detailed description regarding bone formation on computed tomography, which was also indicated by Delawi *et al*.

This prospective, multicenter, randomized study by Delawi *et al*. included 134 patients and compared the effectiveness of ICBG and OP-1 with respect to both clinical success measured by using the Oswestry disability index and radiographic fusion on computed tomography at

1 year postoperatively. Although the noninferiority margin of OP-1 (success of autograft – success of OP-1) was set at 15%, the fusion rate with OP-1 was significantly lower than that with ICBG (54% *vs*. 74%), and noninferiority was not attained.

Although this study has several limitations, such as high smoking rate in the OP-1 group, short follow-up period, and inclusion of patients with degenerative and isthmic spondylolisthesis, there is currently no sufficient evidence to confute the results of this study.

To avoid unnecessary interventions and indiscriminate use of BMPs, patients who will truly benefit from their application (6) should be identified. In addition, the methods in which BMPs can work effectively (carrier or combined with an anabolic agent) also need to be explored (7). Current recommendations for use of BMPs support the 2014 North American Spine Society recommendation: "Based on the available evidence, BMP(-2) is indicated as an adjunct to spinal fusion in cases in which other alternatives are either not available or are not likely to lead to effective fusion (8)."

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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