Meta-analysis of Trials of Recombinant Human Bone Morphogenetic Protein-2: What Should Spine Surgeons and Their Patients Do With This Information?

Spinal fusion is performed to correct spinal instability and is commonly used as an adjunct to decompression. Outcomes of patients with spondylolisthesis and associated stenosis who are treated with decompression and fusion have been convincingly shown to be superior to those of patients treated without surgery, and the beneficial effect is durable through at least 4 years (1). Spinal fusion without decompression has been shown to be effective compared with commonly available medical management in alleviating pain and improving functional capacity in patients with deformity and carefully selected patients with intractable pain due to degenerative disease at 1 or 2 levels (2–4). To enhance the rate of successful fusion, surgeons frequently use graft material. Autologous iliac crest bone graft (ICBG) has been considered the gold standard for grafting, but its use requires harvesting bone from a separate site, which may involve a separate surgery. Although many alternatives exist, recombinant human bone morphogenetic protein-2 (rhBMP-2) is the only one that has shown outcomes similar to those of autologous bone graft (5).

Over the past few years, there has been a whirlwind of controversy in the spine community surrounding the promotion and use of rhBMP-2 for spinal fusion. The clinical findings of the meta-analyses sponsored by the Yale University Open Data Access Project about the efficacy and harms associated with rhBMP-2 are published in this issue (6, 7) and can be summarized as follows. First, there is no evidence of a clinically important difference between rhBMP-2 and autologous ICBG for inducing spinal fusion. Second, both options are associated with similar complication rates when used as graft material in anterior lumbar interbody fusion or posterolateral fusion; this includes neurologic complications and retrograde ejaculation. Many of the complications described in the reports are not related to the graft material used per se but are commonly encountered in the fusion patient population. Third, rhBMP-2 is associated with higher complication rates than autograft in anterior cervical surgery and a higher rate of ectopic bone formation in posterior lumbar interbody fusion. Ectopic bone formation may be associated with neurologic complications. Fourth, although the risk for cancer may be slightly increased in patients receiving rhBMP-2 compared with those receiving autograft, the absolute risk is small and the increased risk is no longer apparent at 4 years. Given the small absolute risk and few cancer cases, the clinical relevance of this finding is questionable.

These findings are important for guiding clinical decision making. On the basis of them, using either autograft or rhBMP-2 to enhance fusion rates in patients having anterior lumbar interbody fusion or posterolateral fusion seems clinically reasonable. Patients should be counseled on the relative benefits and harms of each option and should be allowed to actively participate in decision making. In some procedures, such as anterior lumbar interbody fusion, graft harvest is a separate procedure and avoiding a second incision and associated graft site pain may be well worth the exceedingly small increased risk for cancer. In posterolateral fusion procedures, locally harvested graft and ICBG are often available through the same incision. In these cases, it may not make sense to assume any increased risk, no matter how small. Given the higher complication rates noted in anterior cervical surgery, rhBMP-2 should not be used in this setting without a compelling reason—for example, during a pseudarthrosis repair or other salvage procedure. For posterior interbody procedures, such as posterior lumbar interbody fusion or transforaminal lumbar interbody fusion, the use of rhBMP-2 is associated with ectopic bone formation, and strategies to minimize the clinical effect of excessive bone growth should be used.

One caution in interpreting this information is that patients in the comparator group received autologous ICBG, the gold standard. One cannot assume that other graft materials (for example, allograft, demineralized bone matrix, or ceramic) would have results similar to those of autograft or rhBMP-2. Clinical decision making for cases where autograft is not available would have to take into account the probable lower fusion rates with these alternatives compared with autograft or rhBMP-2 (5).

Another important implication of these studies relates to how surgeons make decisions about the adoption and use of new health care technologies. Many new technologies, such as rhBMP-2, offer the promise of improved clinical outcomes (in this case, enhanced spinal fusion rates). However, in addition to the potential clinical benefits, these technologies come with the potential for increased complication rates and higher costs. Therefore, it is important that clinicians consider not only the efficacy of new technologies, defined as the ability of an intervention to produce the desired beneficial effect in expert hands and under ideal circumstances, but also the effectiveness of the technology, which can be defined as the ability of an intervention to produce the desired beneficial effect in actual practice. Furthermore, clinicians are increasingly being asked to consider the cost of new health care technologies in their clinical decision making.

Early adopters of new technologies are often critical of hospital administrators and payers who scrutinize use of such technologies because of a lack of clinical evidence to
justify the incremental cost associated with their use. These early adopters often cite the difficulties of demonstrating a new technology’s comparative clinical effectiveness that are due to the time lag required for clinical follow-up. However, as Alan Garber, former health economist at Stanford University and the current Provost of Harvard University, has aptly noted, “Since no intervention is assumed to be effective until it has been proved effective, the burden of proof for a new medical intervention is placed on its advocates. Examining the evidence requirement from their point of view is an important step toward understanding its consequences” (8). Furthermore, as Emanuel and colleagues have pointed out, “Novelty cannot be equated with benefit. An intervention’s value resides in its ability to reduce mortality, morbidity, or save money, not in its unique mechanism of action” (9). Therefore, clinicians should embrace patient registries; randomized, controlled trials; observational cohort studies; and other forms of evidence development as they seek to understand the comparative effectiveness of new technologies and provide the highest-value care for their patients.

The role of rhBMP-2 in spinal surgery is still being defined. However, the Yale University Open Data Access Project studies provide valuable insight into the potential benefits and harms associated with its use. Clinicians should carefully weigh the demonstrated and potential benefits and harms as well as the costs when considering the adoption and use of new health care technologies, such as rhBMP-2.

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