Bone Morphogenic Protein Use in Spinal Surgery

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KEYWORDS

• Bone morphogenic protein • Spinal surgery • Fusion • Ethical standards

KEY POINTS

- Bone morphogenic protein (BMP) provides excellent enhancement of fusion in many spinal surgeries.
- BMP should be a cautionary tale about the use of industry-sponsored research, perceived conflicts of interest, and holding the field of spinal surgery to the highest academic scrutiny and ethical standards.
- In the case of BMP, not having a transparent base of literature as it was approved led to delays in allowing this superior technology to help patients.

INTRODUCTION

Spinal surgery has been increasingly used over the last several decades in order to correct structural compression of neural elements. The goal of spinal surgery is 2-fold: to decompress neural elements and to fuse the bony elements surrounding the spine to prevent future instability.

In particular, there are 2 methods used to promote bony fusion across adjacent vertebral elements. The first method is referred to as "instrumentation-induced fusion (IIF)." In this method, hardware is affixed to the bony elements of the spine to immobilize them relative to each other. Fusion then results over several months as bone formation occurs across these immobilized bony elements.

Another method involves the placement of material adjacent to the vertebrae to enhance bone growth, which is referred to as "material-induced fusion (MIF)." Importantly, MIF is completely independent of IIF, and each of these methods can be performed separately from or simultaneously with the other. As an example, "on-lay fusion" techniques represent MIF performed separately from IIF. However, placing pedicle screws and rods in conjunction with iliac bone autograft for lumbar spinal fusion represents the simultaneous use of MIF and IIF techniques. Importantly, the gold standard of MIF is the use of iliac bone autograft to enhance bony fusion. However, iliac bone autograft has been associated with a relatively high morbidity and leads to often unacceptable levels of postoperative pain that can impede recovery and prolong hospital length of stay.

The use of bone morphogenic protein (BMP) has thus been proposed to replace iliac bone autograft to enhance bony fusion. It is important to view the use of BMP within the broad goals of spine surgery: it is one method to enhance arthrodesis. In that context, it is not important to determine if BMP enhances bone growth, but instead it is

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important to determine if BMP promotes arthrodesis at a higher rate than other MIF and IIF approaches within an acceptable safety profile.

BMP itself is a salient topic in spine surgery, primarily because it has gained widespread use. Indeed, many spine surgeons across both neurosurgery as well as orthopedic surgery use BMP as a method of MIF despite the fact that BMP has not gained general US Food and Drug Administration (FDA) approval for this purpose. As a result, most surgeons have adopted the practice of adding the off-label use of BMP to the consenting process for surgery. With such widespread adoption by the spine community without the express sanctioning by the FDA, it remains the responsibility of those in the field of spinal surgery to continuously weigh the risks and benefits of BMP. Such heightened scrutiny is especially needed because BMP has an unclear safety profile, and it is argued to be a nontrivial cause of various numbers of postoperative complications and adverse events.

In this review, the authors first review the development of BMP. Then, they cover the controversy surrounding the role of BMP in the development of bony cancers. Finally, the authors summarize the current state of affairs regarding the use of BMP in spinal surgery.

DEVELOPMENT OF BONE MORPHOGENIC PROTEIN

BMP, or recombinant human bone morphogenic protein-2, was initially discovered in the 1960s by Marshall Urist.[1] It was introduced as a commercial product in 2002 for the purpose of increasing the rate of bony fusion after spinal surgery. Commercially, BMP is used through BMP-impregnated collagen sponges, creating an implantable substance that is placed in the vicinity of bone in order to induce bony fusion. Strong preclinical data supporting the use of BMP to enhance growth of existing bone appeared in the literature in the 1990s.[2] The first human trials testing the correct dosing and the safety profile of BMP occurred in the late 1990s, 2000,[2] and 2002.[3] These data were quickly followed by industry-supported research that endorsed the use of BMP in spinal surgery, and all reported an excellent safety profile. Specifically, Boden and colleagues[4] used BMP in anterior lumbar interbody fusions (ALIFs) in 11 patients and found that BMP enhanced the rate of bony fusion. Boden and colleagues[3] also used BMP in posterior spinal fusions and found a similar result. Burkus and colleagues[5,6] produced several articles using BMP in ALIFs, again finding that BMP led increased rate of fusion. Similarly, many other articles, all reporting on trials that were funded from industry, found similar positive results for BMP and, in general, reported no adverse affects related to BMP.[7–9] Based on these results, a meta-analysis of the use of BMP reported that industry-led research tested the use of BMP on 780 patients and reported a 0% rate of adverse events, suggesting that BMP has at most a 0.5% adverse event rate within 99% confidence intervals.[10]

Based on a subset of these data, BMP was approved by the FDA for use in spinal surgery. However, the use of BMP in spine surgery was approved only for one-level ALIFs with very particular types of cages that were used in the industry-sponsored clinical data. Specifically, the cages had to be tapered and threaded and included a lordotic curvature. Of note, most of the clinical data from the industry trials tested the use of BMP in ALIFs, which explains the reasoning of the FDA to approve BMP for just that purpose. Later on in 2004, the FDA approved the use of BMP in revision surgeries for posterior lateral interbody fusions as well.

After this approval, there were naturally many studies that were geared toward showing that BMP could be safely used in indications other than one-level ALIFs. Thus, this led to the state of affairs from 2010 to the present day in which BMP was frequently used off label for posterior and transforaminal lumbar interbody fusions as well as in thoracic and cervical procedures such as anterior cervical discectomy and fusions (ACDFs).

CONTROVERSY SURROUNDING BONE MORPHOGENIC PROTEIN USE

Based on skepticism of industry-led clinical trials, the incredibly low adverse event rate associated with BMP, the speed with which BMP achieved FDA approval, and the widespread off-label use of BMP in spine surgery, studies began to reexamine the safety profile of BMP.

Concerns first started to mount when anecdotal data supported the idea that BMP use in ACDF led to an increased inflammatory response of cervical prevertebral tissue. This increase in prevertebral soft tissue swelling led to an increased rate of dyspnea and dysphagia in the postoperative period. In severe cases, the increased prevertebral soft tissue swelling led to emergent intubation in order to prevent respiratory collapse.

As a result, these reports and other concerns led to the FDA issuing a public health notification on the use of BMP in June 2008. In that public