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Commentary on research of bone morphogenetic protein discussed in review article: Genetic advances in the regeneration of the intervertebral disc

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Abstract

Background: In Maerz, Herkowitz and Baker's review, Molecular and Genetic Advances in the Regeneration of the Intervertebral Disc, they also included an assessment of both *in vivo* and *in vitro* complications attributed to Bone Morphogenetic Protein ((BMP): BMP-2, BMP-7). This topic is of particular interest to spinal surgeons, as INFUSE/BMP (Medtronic, Memphis, TN, USA) is utilized, mostly off-label in the cervical, thoracic, and lumbar spine, where it has been associated with significant perioperative and postoperative complications.

Methods: BMP-2 and BMP-7 are the only human recombinant growth factors approved by the Food and Drug Administration (FDA) for anterior lumbar interbody fusion (ALIF) in combination with the Lumbar Tapered Fusion Device (LT Cage: Medtronic, Memphis, TN, USA). BMP, however, is more typically utilized "off-label" in many other areas of the spine, where it has been associated with numerous complications.

Results: Maerz, *et al*. documented multiple *in vivo* and *in vitro* laboratory-based animal studies dating back to the early 2000's in which BMP (INFUSE is the clinically available product: Medtronic, Memphis, TN) contributed to multiple complications, especially when utilized at higher doses. These complications included; inflammation/inflammatory processes, increased vascularity, fibroblastic proliferation, and catabolism.

Conclusion: Maerz, *et al*. reviewed the increased risks associated with utilizing high dose BMP=INFUSE in spinal surgery, particularly when utilized "off-label". The authors clearly indicate that BMP/INFUSE should be further investigated (based on the old and new findings) to better determine/confirm its safety, efficacy, and dosing.

Key Words: Animal laboratory studies, bone morphogenetic protein, clinical, infuse, intervertebral disc, regeneration, spinal surgery

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INTRODUCTION

Maerz, Herkowitz, and Baker have written an excellent review article, Molecular and Genetic Advances in the Regeneration of the Intervertebral Disc.[3] Of critical interest to the practicing spinal surgeon was their

presentation of laboratory-documented (*in vivo* and *in vitro* studies) complications attributed to INFUSE/Bone Morphogenetic Protein ((BMP) (Medtronic, Memphis, TN, USA)), some dating back to the mid 2000s.[1-7] More spinal surgeons who predominantly use this product "off-label" have been experiencing more INFUSE/BMP-related complications following spinal fusions. According to Maerz, *et al.* review of the literature, many of these complications were known in the early-mid 2000's.

FOOD AND DRUG ADMINISTRATION "ON-LABEL" VS. "OFF-LABEL" USE OF BONE MORPHOGENETIC PROTEIN

Maerz, *et al.* noted that BMP-2 and BMP-7 (OP-1) are the only human recombinant growth factors (osteoinductive properties) approved by the Food and Drug Administration (FDA).[3] It is, however, rarely used for the FDA approved anterior lumbar interbody fusion (ALIF) in combination with the Lumbar Tapered Fusion Device (LT Cage) (Medtronic, Memphis, TN, USA). It is more typically utilized in an off-label capacity in other areas of the spine, where high dose application is increasingly associated with a myriad of complications. Watts' noted the tragic, unregulated, and uncontained, "no holds barred", "off-label" use of INFUSE/BMP particularly in the anterior cervical spine, and attributed this to a failure in neurosurgical and orthopedic leadership.[7]

IN VITRO, BMP-2 PROMOTES EXPRESSION OF CHONDROGENIC, NOT OSTEOGENIC PHENOTYPES OF HUMAN INTERVERTEBRAL DISC CELLS

BMP-2, *in vitro*, upregulates multiple genes and enhances the expression of many proteins. In 2003, Kim, *et al.* observed how BMP-2 promotes the expression of "chondrogenic, not osteogenic, phenotypes of human intervertebral disc cells," resulting in greater proteoglycan synthesis, the up-regulation of articular chondrocytes, and intervertebral disc cells (IVD).[2] Furthermore, different concentrations of rhBMP-2 were utilized, "without inducing an osteogenic phenotype and/or associated calcifications or mineralizations." They concluded that rhBMP-2 might effectively be utilized to regenerate the matrix of the IVD.

IN VITRO, BMP-2 IS UNTHERAPEUTIC, AND INDUCES APOPTOSIS

In 2011, McCanless, *et al.* evaluated the *in vitro* impact of BMP-2 on cell proliferation/extracellular matrix (ECM) synthesis of the nucleus pulposus (NP)-like differentiated mesenchymal stem cells (MSCs).[4] They found that "BMP-2 induced apoptosis, Collagen I (Col I) accumulation, and aggrecan production hindrance, furthermore, they found it was untherapeutic."

IN VIVO, BMP-2 PROMOTED DEGENERATIVE DISC CHANGES AND OTHER COMPLICATIONS

In an *in vivo* animal model in 2011, Huang, *et al.* showed that rhBMP-2 promoted more degenerative changes in the disc vs. controls, while also resulting in other complications; "increased inflammation, vascularity, and fibroblastic proliferation in rhBMP-2-treated animals compared with saline-treated animals."[1]

IN VITRO BMP-14, AT HIGHER DOSES, PRODUCED MORE COMPLICATIONS

In 2004, Wang, *et al.* noted that the *in vitro* applications of BMP-14 (GDF-5) induced cellular activation/proliferation in primary IVD cells, promoting collagen synthesis. Higher doses produced inflammatory reactions in the adjacent vertebrae and connective tissue that infiltrated the nucleus. This indicated that "the positive effect of GDF-5 may depend on dosing, and that multiple treatments can cause catabolic and/or inflammatory processes."[6]

INSULIN-LIKE GROWTH FACTOR-1 PROMOTED COMPLICATIONS AT HIGHER DOSES

In 2004, Walsh, *et al.* further demonstrated that one injection of insulin-like growth factor-1 (IGF-1) into a degenerate murine disc resulted in increased cell density and proliferation at 1 week, while multiple injections resulted in inflammatory reactions in adjacent vertebrae, indicating a dose-dependent response.[5]

CONCLUSION

In their review article, Maerz, *et al.* discussed how BMP/INFUSE, particularly when applied at higher dosages *in vitro* and *in vivo* models, resulted in multiple adverse reactions.[3] Complications included apoptosis of interverebral disc cells, inflammatory reactions, increased vascularity, fibroblast infiltration, and other catabolic effects. Of interest, some of the reviewed studies were published in the early 2000s, while others are more recent.[1-7] The data highlighted by Maerz, *et al.* indicate that perhaps spine surgeons should reconsider the use of BMP/INFUSE "off-label" to perform spinal fusions. The basic scientists should assist spinal surgeons in the reassessment of BMP/INFUSE, particulary when it comes to assessing its safety, efficacy, and appropriate dosing levels.

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