Commentary: Bone morphogenetic protein’s contribution to pulmonary artery hypertension: Should this raise concern for patients undergoing spinal fusions with bone morphogenetic protein?

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Abstract

Background: Congenital pulmonary artery hypertension (PAH) has been clinically correlated in 70–80% of cases with mutations at the bone morphogenetic protein receptor 2 (BMPR2) genetic site. However, there is also clinical and basic science/laboratory literature indicating a dose–response relationship between BMP signaling and the evolution of PAH (e.g., increased endothelial, smooth muscle, and progenitor cell production, with calcifications).

Methods: Clinical PAH, characterized by pulmonary artery remodeling, elevated right ventricular pressures, increased vascular constriction, and inflammation, is largely due to congenital mutations at the BMPR2 site. Both clinical and laboratory studies have confirmed the correlation between dysfunction at the BMPR2 genetic site and PAH. However, additional basic science and clinical studies suggest a dose–response relationship between BMP signaling and the evolution of PAH.

Results: Laboratory studies found that pulmonary artery smooth muscle cells (PASMCs) under hypoxic conditions proliferated in response to BMP-2 in a dose-dependent fashion. Others noted that PASMCs extracted from patients with Primary Pulmonary Hypertension (PPH) demonstrated abnormal growth responses to transforming growth factor-beta (TGF-β) in a dose-related manner.

Conclusions: The clinical/basic science literature appears to document a dose-dependent relationship between BMP and PAH (independent of the congenital lesions). Does this mean patients undergoing lumbar fusions with BMP are at risk for PAH?

Key Words: Bone morphogenetic protein, pulmonary hypertension, spinal surgery

INTRODUCTION

It is well documented that anomalies at the bone morphogenetic protein receptor 2 genetic site (BMPR2) have been clinically linked to the congenital form of pulmonary hypertension (PAH) (e.g., accounting for 70–80% of cases). However, for BMP that is typically used “off-label” in spinal fusions, reported complications...
Summary: It is well documented that anomalies at the bone morphogenetic protein receptor 2 genetic site have been clinically linked to the congenital form of PAH (e.g., accounting for 70-80% of cases). Therefore, after consulting some of basic science and clinical literature about BMP’s, we ask whether BMP’s used clinically for spinal fusions may risk the evolution of PAH or comparable syndromes.

Clinical/Genetic-based studies of BMPR2-related PAH

Multiple clinical- and genetic-based studies attribute congenital PAH (e.g., defined as pulmonary artery remodeling prompting increased right ventricular systolic pressure [RVSP], vasoconstriction, and inflammation) to the bone morphogenetic protein receptor 2 (BMPR2) site [13,15,17]. Therefore, after consulting some of basic science and clinical literature about BMP’s, we ask whether BMP’s used clinically for spinal fusions may risk the evolution of PAH or comparable syndromes.

Complications of BMP/INFUSE (Medtronic, Memphis, TN, USA) in spinal surgery do not cite Pulmonary Artery Hypertension

The list of clinical complications resulting from spinal fusions utilizing BMP have, thus far, not included PAH [2,3,5,6,12,14,16,18] [Table 2]. Certainly, several authors of spinal series/reviews have compiled lists of the multiple complications associated with using BMP for spinal fusions (mostly “off-label”). Although these include marked dysphagia/intubation/tracheostomy, reoperations, repeat instrumented fusions, seroma with acute neural compression/hematoma/swelling, heterotopic bone formation (heterotopic ossification [HO])/delayed neural compression, osteolysis, pseudarthrosis, infection requiring debridement, thromboembolic events, respiratory distress, arachnoiditis, increased retrograde ejaculation, implant displacement, subsidence, urogenital events, increased radiculitis, poorer global outcomes, and cancer, none have mentioned PAH. In 2013, Carragee et al. found a greater risk of BMP-fused patients developing cancer when they had received higher doses of BMP. Yarmechuk et al. further observed that BMP used in spine surgery (260 with BMP vs. 515 without BMP) was responsible for acute inflammation of the upper airway, and led to respiratory obstruction on postoperative days 2–7. BMP was also responsible for significantly longer hospital stays, higher charges, more tracheotomies/reintubations, greater dysphagia/dyspnea/respiratory failure, more readmissions (e.g., especially to intensive care units [ICUs]), and higher 90-day mortality rates. Notably, in all these studies, PAH was never mentioned as a complication of spinal fusion with BMP.

Changes in the integration of TGF-β may contribute to the pathogenesis of PAH [Table 1]

In an initial study, Morrell et al. found that PASMCs extracted from patients with PAH demonstrated abnormal growth responses to transforming growth factor-beta (TGF-β) (e.g., BMP is a member of that family). Therefore, after consulting some of basic science and clinical literature about BMP’s, we ask whether BMP’s used clinically for spinal fusions may risk the evolution of PAH or comparable syndromes.

| Sections | Summary |
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| Introduction | Summary: It is well documented that anomalies at the bone morphogenetic protein receptor 2 genetic site (BMPR2) have been clinically linked to the congenital form of PAH (e.g., accounting for 70-80% of cases). Therefore, after consulting some of basic science and clinical literature about BMP’s, we ask whether BMP’s used clinically for spinal fusions may risk the evolution of PAH or comparable syndromes. |
| Complications of BMP in Spinal Surgery Do Not Yet Include Pulmonary Artery Hypertension (PAH) | Summary: Many clinical studies utilizing BMP for spinal fusions document multiple complications. These have included: marked dysphagia, intubation, intubation, tracheostomy, reoperations, repeat instrumented fusions, seroma with acute neural compression/hematoma/swelling, heterotopic bone formation (HO), delayed neural compression, osteolysis, pseudarthrosis, infection requiring debridement, thromboembolic events, respiratory distress, arachnoiditis, increased retrograde ejaculation, implant displacement, subsidence, urogenital events, increased radiculitis, poorer global outcomes, and cancer, but not yet PAH. |
Summary: Both clinical and laboratory studies indicate that BMP’s may promote dose-dependent changes in pulmonary arterial hypertension and impacts endothelial, smooth muscle cells (SMCs), and progenitor cells related to PAH.¹⁹

\( \beta \): Transforming growth factor-beta

ACDF: Anterior cervical discectomy and fusion, AE: Adverse events, ALIF: Anterior lumbar interbody fusion, BMP: Bone morphogenetic proteins, BMPR2: Bone morphogenetic protein receptor 2 genetic site, BMP-7: Bone morphogenetic proteins, EC: Endothelial cell, HDMEC: Human dermal microvascular endothelial cells, HO: Heterotopic ossification, ICU: Intensive care unit, IPH: Idiopathic Pulmonary Hypertension, PAH: Pulmonary hypertension, PASMC: Pulmonary artery smooth muscle cells, PLF: Posterolateral lumbar fusion, PLIF: Posterior lumbar interbody fusion, PPH: Primary pulmonary hypertension, rhBMP-2: Bone morphogenetic protein, RVSP: Right ventricular systolic pressure, SMC: Smooth muscle cell, TGF-β: Transforming growth factor-beta

of familial PAH, but also observed that BMP plays a significant role in “dysfunctional BMP signaling” and impacts endothelial, smooth muscle cells (SMCs), and progenitor cells related to PAH.¹⁹
Table 2: Summary of Bone Morphogenetic Protein-2 (BMP-2) and Pulmonary Artery Hypertension (PAH) Interactions

| Complications of BMP in spinal surgery do not yet include pulmonary artery hypertension (PAH) | Acute airway obstruction following cervical spinal surgery with BMP |
| Pulmonary arterial hypertension and BMP’s | Altered growth responses of pulmonary artery smooth muscle cells due to PAH related to TGF-beta and BMP |
| Role of BMP receptor in the development of pulmonary hypertension | BMP-2 signaling promotes pulmonary PAH |
| BMP induced cell proliferation leads to hyperproliferation of pulmonary artery smooth muscle cells and PAH | BMP-2 contributes to apoptosis of pulmonary artery smooth muscle cells under hypoxia |
| BMP-2 promotes calcification of human vascular smooth muscle cells | Prolonged ectopic calcification induced by BMP-2-derived synthetic peptide |
| BMP expression in human atherosclerotic lesions | Role of BMPs in endothelial cell function/vulnerability |

PAH: Pulmonary hypertension, BMP: Bone morphogenetic proteins, TGF: Transforming growth factor

Dose-dependent impact of BMP-2 on pulmonary artery smooth muscle cells and vascular calcification

BMP-2 may promote dose-dependent changes in pulmonary SMCs and vascular calcification leading to PAH [1,4,7,10,11] [Table 1]. Pi et al. evaluated how BMP-2 “regulates phosphatase and tensin homologue deleted on chromosome ten (PTEN) and apoptosis of PASMCs under hypoxia.”[10] They observed that PASMCs proliferated in response to BMP-2 administered in a dose-dependent fashion. Li et al. further observed that BMP-2 is a strong osteogenic protein that promotes osteoblast differentiation and bone formation contributing to vascular calcification.[7] When they evaluated the impact of BMP-2 on human SMC calcification in vitro, the BMP-2 dose stimulated phosphate uptake in a dose-related fashion. Saito et al. observed that BMP-2 promotes bone and cartilage formation, contributes to ectopic calcification and a proliferation of osteoblast-like cells, and “organogenesis and apoptosis.”[11] Bostrom et al. looked at arterial wall calcification/atherosclerosis and the resultant mature bone formation including marrow within these vascular tissues.[1] Here, BMP-2 was expressed in the calcification found in human plaques, and cells cultured from calcified aortic walls/nodules; they found cells with “immunocytochemical features characteristic of microvascular pericytes that were capable of osteoblastic differentiation.” Dyer et al. also noted that BMPs play a role in vascular endothelial growth and angiogenesis.[4]

CONCLUSIONS

Clinical studies cited mutations at the BMPR2 genetic site as responsible for congenital PAH (70–80% of cases). However, both clinical and laboratory studies showed that BMPs may promote dose-dependent changes in pulmonary SMCs and vascular calcifications within vessel walls, which may lead to PAH.

For the purposes of a spine surgeon, this review raises the concern whether patients undergoing BMP-supplemented spinal fusions may be potentially exposed to developing PAH? As yet, this question remains unanswered, and it could take decades to know the answer. However, just being aware of the potential risk for developing PAH in patients undergoing spinal fusions (most “off-label”) utilizing BMP may curtail or eliminate its use.

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