Surgical Neurology International

SNI: Spine, a supplement to Surgical Neurology International

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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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Received: 28 August 14 Accepted: 21 October 14 Published: 30 December 14

This article may be cited as:
Epstein NE. Commentary: Bone morphogenetic protein's contribution to pulmonary artery hypertension: Should this raise concern for patients undergoing spinal fusions with bone morphogenetic protein?. Surg Neurol Int 2014;5:S570-3.
Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2014/5/16/570/148050

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

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/2152-7806.148050

Quick Response Code:

INTRODUCTION

It is well documented that anomalies at the bone morphogenic 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

(e.g. heterotopic bone formation, osteolysis, infection, and seroma/hematoma with attendant neurological deficits, and others) have not yet included PAH. Nevertheless, there is cause for concern, since laboratory studies like that performed by Pi *et al*. found that pulmonary artery smooth muscle cells (PASMCs) under hypoxic conditions proliferated in response to BMP-2 in a dose-dependent fashion.[10] Furthermore, 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).[8] Therefore, after consulting some of the basic science and clinical literature about BMPs, should we be concerned that BMPs used clinically for spinal fusions expose patients to the risk of developing PAH or related 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/hematomas/swelling, heterotopic bone formation (heterotopic ossification [HO])/delayed neural compression, osteolysis, pseudarthrosis, infection requiring debridements, thromboembolic events, respiratory distress, arachnoiditis, increased retrograde ejaculation, cancer, implant displacement, subsidence, urogenital events, increased radiculitis, and poorer global outcomes, none have mentioned PAH.[2,3,5,6,16] In 2013, Carragee *et al*. found a greater risk of BMP-fused patients developing cancer when they had received higher doses of BMP.[3] 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.[18] 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.

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] [Table 2]. West *et al*. noted that the mutation responsible for congenital PAH (e.g., up to >80% of the time) was related to the BMPR2 genetic site.[15] Teichert-Kuliszewska *et al*. further observed that mutations in BMP and BMPR2 occur in patients with idiopathic pulmonary arterial hypertension (IPAH), but that their modes of interaction remain undefined.[13] Their working hypothesis was: "Loss-of-function mutations in BMPR2 could lead to increased pulmonary endothelial cell (EC) apoptosis, representing a possible initiating mechanism in the pathogenesis of pulmonary arterial hypertension." Yamanaka *et al*. further attributed the onset of PAH to hyperproliferation of the PASMC, leading to greater endothelial injury.[17] When they evaluated BMP and other vasoactive factors related to PAH (e.g. endothelin [ET], angiotensin II [Ang II], and aldosterone), they discovered that BMP-2, BMP-7, and BMP ligands (not BMP-4 or BMP-6), "significantly increased cell mitosis in both PASMC cell types."

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 TGF-β, and that changes in the integration of TGF-β appeared to contribute to the pathogenesis of PAH.[8] In a second study, Morrell confirmed that mutations related to BMP type II receptors were associated with the onset of most cases

Table 1: Summaries

Sections	Summary
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/hematomas/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.[2,3,5,6,12,14,16,18]

Continud...

Table 1: Continud...

Sections	Summary
Acute airway obstruction following cervical spinal surgery with BMP	Summary: Yaremchuk *et al.* found that BMP used in cervical spine surgery resulted in higher complications rates particularly regarding pulmonary decompensation (days 2-7; more tracheotomies/reintubations, greater dysphagia/dyspnea/respiratory failure, more readmissions/ICU admissions ($P=0.001$), and higher 90-day mortality rates).[18] Again, there is nothing said about whether there is any long-term impact of using BMP in these fusions, and no mention of a relationship/correlation with the evolution of pulmonary hypertension.
Pulmonary arterial hypertension and BMP's	Summary: West *et al.* defined pulmonary arterial hypertension (PAH) as attributable to pulmonary artery remodeling, resulting in "increased right ventricular systolic pressure (RVSP), vasoconstriction and inflammation."[15] Notably, over 80% of cases are congenital, attributable to mutations at the bone morphogenetic protein receptor 2 genetic site (BMPR2).
Altered Growth Responses of Pulmonary Artery Smooth Muscle Cells due to PAH related to TGF-beta and BMP	Summary: Morrell *et al.* looked at mutations for bone morphogenetic protein (BMPR-II) as contributors to PPH (primary pulmonary hypertension) and concluded "growth signals may contribute to the pathogenesis of primary pulmonary hypertension PPH."[8]
Role of BMP Receptor in the Development of Pulmonary Hypertension	Summary: Morrell noted that mutations related to BMP type II receptors were associated with the onset of most cases of familial pulmonary arterial hypertension (PAH).[9] He observed that BMP has both a role in, "dysfunctional BMP signaling" and impacts endothelial, smooth muscle cell, progenitor cells" related to PAH.
BMP-2 Signaling Promotes Pulmonary PAH	Summary: Teichert-Kuliszewska *et al.* observed that mutations in BMP and BMPR2 occur in patients with idiopathic pulmonary arterial hypertension (IPAH).[13] This study supported the hypothesis that "loss-of-function mutations in BMPR2 could lead to increased pulmonary endothelial cell EC apoptosis, representing a possible initiating mechanism in the pathogenesis of pulmonary arterial hypertension."
BMP Induced Cell Proliferation Leads to Hyperproliferation of Pulmonary Artery Smooth Muscle Cells and PAH	Summary: Yamanaka *et. al*. noted the genetic studies linking" familial and idiopathic pulmonary arterial hypertension (PAH)" to BMPRII mutations.[17] They found that BMP-2, BMP7, and BMP ligands (not BMP-4 or BMP-6), "significantly increased cell mitosis in both PASMC cell types."
BMP-2 Contributes to apoptosis of pulmonary artery smooth muscle cells under hypoxia	Summary: Pi *et al.* evaluated how BMP-2 "regulates phosphatase and tensin homologue deleted on chromosome ten (PTEN) and apoptosis of pulmonary artery smooth muscle cells (PASMCs) under hypoxia".[10] They observed that PASMCs proliferated in response to BMP-2 administered in a dose dependent fashion.
BMP-2 Promotes Calcification of Human Vascular Smooth Muscle Cells	Summary: Li *et al.* observed that vascular calcification correlated with a greater risk of cardiovascular events that most commonly are fatal in patients with end-stage renal failure.[7] BMP-2 is a strong osteogenic protein that promotes osteoblast differentiation and bone formation contributing to such vascular calcification. They concluded, "BMP-2 may promote vascular calcification via increased phosphate uptake and induction of osteogenic phenotype modulation in SMC."
Prolonged Ectopic Calcification Induced by BMP-2-Derived Synthetic Peptide	Summary: Saito *et al.* observed that BMP-2 "promotes the formation and regeneration of bone and cartilage, and therefore constitutes the most promising candidate for a bone repair material."[11] Here, the authors evaluated a novel synthetic peptide closely related to residues 73-92 of BMP-2; it induced ectopic calcification and a proliferation of osteoblast-like cells.
BMP Expression in Human Atherosclerotic Lesions	Summary: Bostrom *et al.* looked at arterial wall calcification/atherosclerosis and the resultant mature bone formation including marrow within these vascular tissues; they found cells with " immunocytochemical features characteristic of microvascular pericytes that are capable of osteoblastic differentiation.[1]
Role of BMPs in endothelial cell function/dysfunction.	Summary: Dyer *et al.* noted that BMP's play a role in vascular endothelial growth and angiogenesis.[4] However, alterations in BMP levels are linked to vascular pathologies that include pulmonary hypertension and atherosclerosis.
Conclusion	Summary: Both clinical and laboratory studies indicate that BMP's may promote dose-dependent changes in pulmonary smooth muscle cells and contribute to vascular calcifications which may lead to PAH. For the purposes of a spine surgeon, this review raises the substitute question whether patients undergoing BMP-supplemented spinal fusions may be potentially be 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.

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-4: Bone morphogenetic proteins, BMP-6: Bone morphogenetic proteins, 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.[9]

Table 2: Summary of Bone Morphgenetic 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 functionw/dysfunction

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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