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Review Article

A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned

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Abstract

BACKGROUND CONTEXT: Increasingly, reports of frequent and occasionally catastrophic complications associated with use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in spinal fusion surgeries are being published. In the original peer review, industry-sponsored publications describing the use of rhBMP-2 in spinal fusion, adverse events of these types and frequency were either not reported at all or not reported to be associated with rhBMP-2 use. Some authors and investigators have suggested that these discrepancies were related to inadequate peer review and editorial oversight.

PURPOSE: To compare the conclusions regarding the safety and related efficacy published in the original rhBMP-2 industry-sponsored trials with subsequently available Food and Drug Administration (FDA) data summaries, follow-up publications, and administrative and organizational databases.

STUDY DESIGN: Systematic review.

METHODS: Results and conclusions from original industry-sponsored rhBMP-2 publications regarding safety and related efficacy were compared with available FDA data summaries, follow-up publications, and administrative and organizational database analyses.

RESULTS: There were 13 original industry-sponsored rhBMP-2 publications regarding safety and efficacy, including reports and analyses of 780 patients receiving rhBMP-2 within prospective controlled study protocols. No rhBMP-2–associated adverse events (0%) were reported in any of these studies (99% confidence interval of adverse event rate <0.5%). The study designs of the industry-sponsored rhBMP-2 trials for use in posterolateral fusions and posterior lateral interbody fusion were found to have potential methodological bias against the control group. The reported morbidity of iliac crest donor site pain was also found to have serious potential design bias. Comparative review of FDA documents and subsequent publications revealed originally unpublished adverse events and internal inconsistencies. From this review, we suggest an estimate of adverse events associated with rhBMP-2 use in spine fusion ranging from 10% to 50% depending on approach. Anterior cervical fusion with rhBMP-2 has an estimated 40% greater risk of adverse events with rhBMP-2 in the early postoperative period, including life-threatening events. After anterior interbody lumbar fusion rates of implant displacement, subsidence, infection, urogenital events, and retrograde ejaculation were higher after using rhBMP-2 than controls. Posterior lumbar interbody fusion use was associated with radiculitis, ectopic bone formation, osteolysis, and poorer global outcomes. In posterolateral fusions, the risk of adverse effects associated with rhBMP-2 use was equivalent to or greater than that of iliac crest bone graft harvesting, and 15% to 20% of subjects

FDA device/drug status: Some rhBMP-2 uses in this article are approved; others are not. See text for details.

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reported early back pain and leg pain adverse events; higher doses of rhBMP-2 were also associated with a greater apparent risk of new malignancy.

CONCLUSIONS: Level I and Level II evidence from original FDA summaries, original published data, and subsequent studies suggest possible study design bias in the original trials, as well as a clear increased risk of complications and adverse events to patients receiving rhBMP-2 in spinal fusion. This risk of adverse events associated with rhBMP-2 is 10 to 50 times the original estimates reported in the industry-sponsored peer-reviewed publications.

Keywords: Critical review; rhBMP-2 trials; Spinal fusion; Safety concerns; Conflict of interest

Introduction

Spinal fusion techniques have historically used autogenous bone grafting, either from local or distant sources, to augment the local techniques used to stimulate fusion. For long spinal fusions or spinal fusions in adverse metabolic or local conditions, traditional techniques of bone grafting can prove inadequate. Accordingly, bone graft substitutes and enhancers have been developed over time to address these needs. One such bone graft substitute, recombinant human bone morphogenetic protein-2 (rhBMP-2), was introduced commercially in 2002.

There has been an appreciation in the more recent spine surgery literature that frequent and occasionally catastrophic complications are associated with the use of rhBMP-2 in spinal fusion surgeries. Adverse events of this sort were not reported as being associated with rhBMP-2 application in multiple early industry-sponsored trials published in peer-reviewed journals. This article critically reviews the evolving safety profile of rhBMP-2; beginning with the original industry-sponsored publications and progressing to later independent assessments of the product and by independent reassessment of publicly available trial data.

In addition to giving perspective to the specific morbidities of rhBMP-2, it is hoped that lessons can be learned from this era in spinal research and publication. Such lessons might prove valuable in the future, allowing us to better serve not only our community of researchers and clinicians but especially our patients who rely on the expeditious but safe introduction of new technologies in health care.

Summary of events leading to the current review

Multiple studies in the 1990s suggested that bone morphogenetic protein-2 (BMP-2) could cause bone induction in various animal models. There was uncertainty, however, regarding appropriate dosing, appropriate carriers, and safety, all of which appeared to be highly variable depending on the species of animal and location of BMP application [1].

When the use later began in humans, there seemed little doubt that bone induction would be possible; but proper dosing and possible adverse reactions with various applications remained uncertain. Preliminary human trials for lumbar fusion were published beginning in 2000 [2] and 2002 [3]. It was clear at the time that the nature and diversity of adverse events could not be well predicted given that rhBMP-2 appeared to be involved in a multiplicity of physiological and pathological events including, but not limited to, the inflammatory response, bone induction and resorption pathways, abnormal growth signaling pathways, certain malignancy pathways, and induction of an altered immune response [1,4]. Accordingly, in a 2002 review article, Poynton and Lane [4] wrote:

> ''Safety issues associated with the use of bone morphogenetic proteins in spine applications include the possibility of bony overgrowth, interaction with exposed dura, cancer risk, systemic toxicity, reproductive toxicity, immunogenicity, local toxicity, osteoclastic activation, and effects on distal organs.''

The results of several small and large industry-sponsored trials were subsequently published [2,3,5–11]. These reported the use of rhBMP-2 in larger numbers of patients undergoing a variety of spinal fusion techniques, including anterior interbody lumbar fusion (ALIF), posterolateral lumbar fusion (PLF), posterior lumbar interbody fusion (PLIF), and anterior cervical discectomy and fusion (ACDF) (Table 1).

Notably, with each new industry-sponsored trial publication, the safety findings were identical: no adverse events associated with rhBMP-2 were reported to be observed. Given that 780 patients received rhBMP-2 in these industry-sponsored publications and that not a single adverse event had been reported, the estimated risk of rhBMP-2 use could be calculated to be less than 0.5% with 99% certainty. That is, the reported risk of an adverse event with rhBMP 2, based on the industry-sponsored data, was less than one-fortieth the risk of a course of commonly used anti-inflammatory or antibiotic medications [12].

Although initially contemplated as an adjunct to spine arthrodesis to be used in particularly adverse clinical situations, a generalized use of rhBMP-2 was observed [13]. In the United States alone, the usage of BMP increased from 0.7% of all fusions in 2002 to 25% of all fusions in 2006, with 85% being used in single- or two-level fusions [14]. By 2007, more than 50% of primary ALIF, 43% of PLIF/transforaminal lumbar interbody fusion (TLIF), and 30% of PLF were reported to use rhBMP-2 [15]. It has been suggested [16] that, at least in part, the documented rapid increase in rhBMP-2 use in spinal surgery was related to the industry-sponsored trials, which reported virtually no