

Bone Morphogenetic Protein use in Spinal Surgery

Castellvi Spine 2016

William C. Welch, MD
 Professor and Chief
 Department of Neurosurgery
 Pennsylvania Hospital

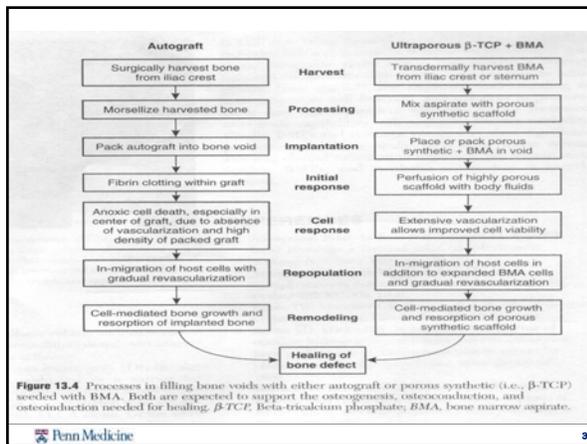


Disclosures

- ◆ Transcendental Spine



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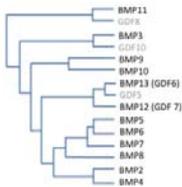
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Bone Morphogenic Proteins

- BMP's are part of the transforming growth factor - beta super family
- Recombinant DNA technology has allowed for mass production of multiple BMP's
- rhBMP-7 (OP-1) and rhBMP-2 (InFuse) are most heavily studied

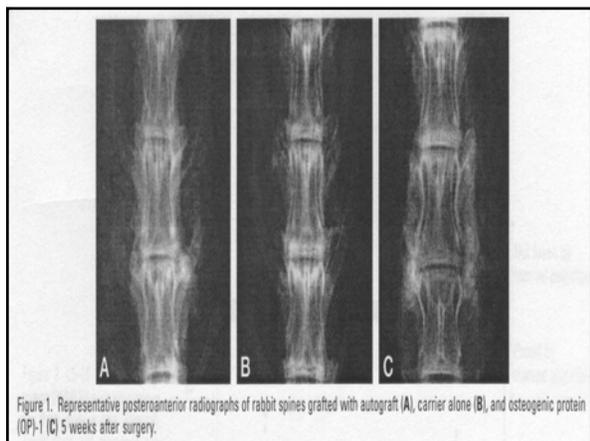
BMP's

- Multifunctional cytokines
- TGF-B superfamily
- Cell growth, differentiation, embryonic pattern formation
- 20 known BMP's including growth/differentiation factors (GDF's)
- Bone and cartilage growth



BMP-7

- Grauer et al reported in 2001 (Spine) a study of single level intertransverse process lumbar fusions using a New Zealand White rabbit model
 - 63% autograft fusion
 - 100% OP-1 fusion
 - Histologically autograft was fibrocartilage while the OP-1 was predominately maturing bone



BMP-7

- ◆ **A pilot study on rhBMP-7 (OP-1) published in Spine by Vaccaro et al**
 - Performed 36 single level uninstrumented posterolateral lumbar fusions
 - Found similar radiographic and clinical success rates between OP-1 and autograft
 - They also no adverse reactions on 1 yr f/u
- ◆ **A larger pivotal trial was not adequately supportive of wider spread OP-1 use**

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BMP-2

- **Only commercially viable product**
 - In 2002, rhBMP-2 (Infuse; Medtronic) was approved for anterior lumbar interbody fusions (ALIFs) with a lumbar fusion device.^[8]
 - In 2008 it was approved to repair posterolateral lumbar pseudarthrosis, open tibia shaft fractures with intramedullary nail fixation.^[9]
- **Several animal studies have all shown rhBMP-2 to induce fusion more rapidly than autograft and have a lower pseudarthrosis rate**
- **Thousands of studies examining BMP mechanism of action/biology/structure**
- **Hundreds of studies related to clinical BMP-2 use**
- **20+ years of clinical use**
- **Over 1,000 lawsuits**

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BMP-2 Effectiveness

- **Agarwal et al *Journal of Neurosurgery*: Spine 11: 729-740, 2010**
 - Meta analysis of publications of osteoconductive bone graft substitutes for lumbar spine surgery
 - 732 studies, 17 met review criteria
 - Trials of rhBMP-2 suggested reductions in the operating time and surgical blood loss, with less effect on the length of hospital stay.
 - There was no difference in radiographic nonunion with the use of rhBMP-7 when compared with AIBG (relative risk 1.02, 95% CI 0.52-1.98).
 - Neither rhBMP-2 nor rhBMP-7 demonstrated a significant improvement on the Oswestry Disability Index when compared with autologous iliac crest bone graft
 - Some publication bias was noted

BMP-2 Safety

- **Carraggee et al *Spine J* 11:471-479, 2011**
 - 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.
 - 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. Meta analysis of publications of osteoconductive bone graft substitutes for lumbar spine surgery
 - This risk of adverse events associated with rhBMP-2 is 10 to 50 times the original estimates reported in the industry-sponsored peer-reviewed

BMP-2 Issues

- **US Senate Committee on Finance (Baucus/Grassley)**
- **“These reports that doctors conducting medical trials while on Medtronic’s payroll may have hidden serious side effects for patients are deeply troubling,”** said Senate Finance Committee Chairman Baucus.
- Ectopic bone formation
- Sterility

BMP-2 Safety

- **FDA Public Health Notification: Life-threatening Complications Associated with Recombinant Human Bone Morphogenetic Protein in Cervical Spine Fusion (7/1/2008)**
- This is to alert you to reports of life-threatening complications associated with recombinant human Bone Morphogenetic Protein (rhBMP) when used in the cervical spine. **Note that the safety and effectiveness of rhBMP in the cervical spine have not been demonstrated and these products are not approved by FDA for this use.**
- Considered a “Black-box” warning

BMP-2 Safety

- **Bodalia et al Bone and Joint Res April 2016 Effectiveness and safety of recombinant human bone morphogenetic protein-2 for adults with lumbar spine pseudarthrosis following spinal fusion surgery**
- Systemic review
- A total of six studies (three prospective and three retrospective) reporting on the use of BMP2 met the inclusion criteria (203 patients).
- Of these, four provided a comparison of BMP2 and bone graft whereas the other two solely investigated the use of BMP2. The primary outcome was seen in 92.3% (108/117) of patients following surgery with BMP2. Although none of the studies showed superiority of BMP2 to bone graft for fusion, its use was associated with a statistically quicker time to achieving fusion. BMP2 did not appear to increase the risk of complication.

BMP-2 Safety

- **Simmonds et al Ann Int Med 158:877-89, 2013**
 - Meta analysis of publications of osteoconductive bone graft substitutes for lumbar spine surgery
 - Individual participant data from 11 of 17 trials sponsored by Medtronic and 1 of 2 other eligible trials were included
 - At 24 months, rhBMP-2 increases fusion rates, reduces pain by a clinically insignificant amount, and increases early postsurgical pain compared with ICBG.
 - Evidence of increased cancer incidence is inconclusive

BMP-2 Conclusions

- **After all is said and done**
 - Reasonably safe product when used per FDA indications
 - Ectopic bone formation
 - Can be unsafe when used off label
 - Cervical spine surgery
 - TLIF
 - As effective as iliac crest autologous bone graft

