Bone Morphogenetic Protein use in Spinal Surgery

Castellvi Spine 2016
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Disclosures

- Transcendental Spine

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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

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
  - In 2008 it was approved to repair posterolateral lumbar pseudarthrosis, open tibia shaft fractures with intramedullary nail fixation
- 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
## 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

- **Carragge 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

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### 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.

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### 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