

**Fu R, Selph S, et al. Effectiveness and Harms of Recombinant Human Bone Morphogenetic Protein-2 in Spine Fusion. Ann Intern Med 2013;158:890-902.**

Design: meta-analysis of randomized clinical trials and cohort studies

PICOS:

- Patient population: patients undergoing spinal fusion in trials sponsored by Medtronic, the manufacturer of INFUSE (rh-BMP-2)
- Intervention: use of rh-BMP-2 during spinal fusion surgery
- Comparison intervention: Iliac Crest Bone Graft (ICBG) during spinal fusion surgery
- Outcomes: effectiveness of rh-BMP-2 as measured by overall success at 24 months and by fusion
  - o Success was defined by multiple criteria, all of which had to be satisfied in order for an outcome to be defined as a success
    - Radiographic fusion by CT or XR showing bone growing continuously through the cage and connecting with vertebral bodies above and below
    - Improvement in Oswestry score
    - Maintenance or improvement in neurologic status
    - No serious adverse event
    - No additional surgical procedure
    - No missing data—this criterion was added by the authors to the definition of success used by Medtronic; patients meeting some success criteria but missing data for other criteria were classified as failures
    - Effectiveness outcomes were calculated at 6 weeks and at 3, 6, 12, and 24 months after surgery
    - Harm outcomes were calculated at operative and up to 4 weeks postoperative, and again at up to 24 months postoperative
  - o A second outcome in addition to the clinical success was the assessment of reporting biases in published articles of industry-sponsored studies
- Study types: for effectiveness and harms, randomized controlled trials plus cohort studies; for harms, the authors also included uncontrolled intervention series
  - o They excluded studies which combined results of rh-BMP-2 with those of other bone morphogenetic proteins unless they could determine that rh-BMP-2 was predominantly used

Study selection and evaluation:

- Four distinct data sources were used

- Medtronic individual patient data (IPD), related protocols, and data dictionaries
- Medtronic internal reports
- Documents from the FDA website
- Literature search
  - Literature databases were MEDLINE, EMBASE, the Cochrane Library, Scopus, clinicaltrials.gov, and the FDA web site through August 2012
- Analyses were stratified by spinal area (lumbar or cervical) and by surgical approach
  - Only studies of anterior lumbar interbody fusion (ALIF) and posterolateral fusion (PLF) had sufficient data for meta-analysis, which were based on IPD from the Medtronic-sponsored trials
  - Data were also available for 1 trial of rh-BMP-2 in cervical spine fusion
- Rating of the strength of evidence was based on risk of bias, consistency, directness, and precision of the data

#### Results:

- There were 13 RCTs sponsored by Medtronic (n=1879) and 1 RCT sponsored by Norton Healthcare (n=102)
- All studies compared rh-BMP-2 with ICBG except for one study which compared rh-BMP-2 with artificial disc replacement
- Lack of blinding was the main source of bias, but the unblinded (patient-reported) outcomes for pain and function were ascertained with well-designed questionnaires
- For harms, studies used broad classifications for many events and generally did not actively elicit information on adverse effects through specific questionnaires
  - For example, retrograde ejaculation was not clearly defined and it was not clear whether investigators asked specifically about it
  - Radiculitis was not defined in any trial, and may have been classified as back pain, leg pain, neurological events, or spinal events
- Five RCTs of rh-BMP-2 vs. ICBG in the setting of ALIF provided moderate-strength evidence of no consistent differences between interventions for overall success, fusion rates, or other effectiveness measures from 6 weeks to 24 months after surgery
  - However, the physical component score of the SF-36 was higher by 3 points (on a 100 point scale) in the rh-BMP-2 group than in the ICBG group
- Adverse events were common in both interventions, but meta-analysis showed no significant differences between groups for any specific adverse event
  - The confidence intervals were wide for differences in occurrence of adverse events, including retrograde ejaculation and subsidence
- Four RCTs of rh-BMP-2 vs. ICBG similarly provided moderate evidence of no consistent difference between interventions for effectiveness or adverse events

- The single trial of rh-BMP-2 in anterior cervical spine fusion had only 33 patients, and found no difference in effectiveness between rh-BMP-2
  - o However, rh-BMP-2 in that study had a higher risk of adverse events at 24 months compared to ICBG; the rate ratio for adverse events was 2.88 for all adverse events
  - o Estimates of the frequency of dysphagia were sensitive to the definitions used; the estimates ranged from 5% to 60% of patients developing the condition
- Five Medtronic-sponsored trials reported 18 cancer cases (633 total patients) through 24 months, compared with 6 cases (817 total patients) in the ICBG groups, for a statistically significant odds ratio of 3.45; at 48 months, there were no statistically significant differences in cancer occurrence between groups
- The second principal aim of the meta-analysis was to compare the published results of rh-BMP-2 with the results from the IPD results
  - o The authors found evidence that Medtronic had reported results in a way which favored rh-BMP-2 but which were to some extent misleading
  - o For example, Medtronic reported results for rh-BMP-2 in one site (n=22) which was part of a larger study in which 137 patients had rh-BMP-2 in the setting of laparoscopic ALIF
    - The 22 patients in that one site had a 100% fusion rate
    - This perfect success rate was not representative of the study as a whole
    - Seven other Medtronic-sponsored studies cited the article with 22 patients instead of the study with the overall results
  - o Medtronic underreported the occurrence of adverse events with rh-BMP-2 even though 7% of rh-BMP-2 recipients had serious adverse events which were possibly device-related

Authors' conclusions:

- In spinal fusion, rh-BMP-2 and ICBG seem to be similarly effective when used in ALIF and PLF; current evidence precludes conclusions about effectiveness in other surgical approaches
- The physical component score of the SF-36 was 3 points better for rh-BMP-2 than for ICBG, but on a scale of 100 points, a 3 point difference falls short of what is clinically meaningful
- In cervical fusion, rh-BMP-2 presents increases in adverse events such as wound healing, dysphagia, and dysphonia
- Data on retrograde ejaculation, urine retention, subsidence, and ectopic bone formation was too sparse to provide estimates of harms associated with rh-BMP-2
- Journal publications of industry-sponsored studies selected analyses and results which favored rh-BMP-2 over ICBG

- Journal practices for sponsored supplements, trial registration, and conflict of interest disclosures may have contributed to publication of an incomplete and sometimes misleading evidence base
- No studies were found which were truly independent of the rh-BMP-2 manufacturer
- There was insufficient information to assess the effects of dose of rh-BMP-2 on harms and benefits
- It is difficult to identify clear indications for rh-BMP-2 in spinal fusion with currently available evidence

Comments:

- The overall analysis, based on access to individual patient data (published and unpublished studies), lends support to the principal conclusion that the advantages of rh-BMP-2 over ICBG are likely to fall short of what was implied in the industry-sponsored comparisons of the two fusion interventions
- The rating system for articles was an unclear blend of criteria used by the Cochrane Back Review Group and the US Preventive Services Task Force
  - The USPSTF document cited by the authors was published in 2001 even though an updated version of the USPSTF evidence system was published in 2007
- Although the authors document some evidence of efforts by Medtronic to present the results of its product in a more favorable light than was warranted, the magnitude of the distortion is not clear in all cases
  - For example, Medtronic cited the results of a single site (Kleeman 2001) with a small number of patients (n=22) with 100% fusion success, even though the “overall results” were less favorable
  - The overall results of the study for rh-BMP-2 in the setting of laparoscopic ALIF (Burkus 2003) were 94.4 success at 24 months, less than 100% but not a very large distortion of the results
- There are small departures from some of the numbers in articles cited by the authors, but these are not serious departures
  - For example, the “large fair-quality cohort study (n=27,067) cited on page 896 in the context of cervical fusion adverse events was Cahill 2009, whose Table 2 shows odds ratios for complications of 1.55 rather than 1.43, and odds ratios of 1.80 rather than 1.63 for dysphagia/dysphonia
- The authors appropriately declined to draw conclusions about the risk of cancer with rh-BMP-2, since their Appendix Table 4 is of dubious value
  - The time frame of 24 months is implausibly short for the induction time for most tumors, several of which were diagnosed less than 12 months after surgery

- If rh-BMP-2 were causative of cancer of any type, the odds ratio would be more apparent at 48 months than at 24 months; this is not the case, and cancer as a consequence of rh-BMP-2 is not supported by current data
- Breast, lung, and prostate cancers are sometimes diagnosed within one year of general health care (non-surgical) consultation for musculoskeletal pain, and are among the cancers which commonly metastasize to bone; the cancers of lung, prostate, and bone seen in the first two years after spine fusion may have been present at the time of surgery (Jordan 2013)
  - For example, men in the UK who consulted their doctors for back pain were 5.3 times as likely to be diagnosed with prostate cancer in the following year than were similar men who did not see their doctors for back pain)
- The equivalence of rh-BMP-2 is supported in comparison to ICBG, but other comparisons (e.g., with bone graft substitutes) is not implied and should not be inferred
- Some comments on the comparisons of rh-BMP-2 with ICBG were noted by spine surgeons but not discussed by the authors; specifically, that in the Medtronic sponsored trials, the ICBG control groups were stopped by the study protocol from taking measures commonly taken by surgeons in normal clinical practice when ICBG is being used to promote fusion, such as the use of local bone graft and decortication of the facet joints; insofar as these could have played a role, they would have made the results of ICBG less favorable in the comparisons with rh-BMP-2
- There is a brief mention of off-label use of BMP in the setting of PLIF, which does not cite Wong et al 2008, in which ectopic bone was documented to have adverse clinical effects with neurological signs; this would provide further arguments against off-label use of BMP

Assessment: High quality meta-analysis supporting good evidence that in the setting of ALIF and PLF, rh-BMP-2 presents no clinically important advantages over bone graft with ICBG; good evidence that it increases the risks of dysphagia, dysphonia, and other postoperative complications in the setting of anterior cervical fusion; but leaves uncertainty regarding the risks of cancer associated with the use of BMP in spine fusion of any type, and uncertainty about the comparative risks of retrograde ejaculation sometimes attributed to BMP

#### References:

Burkus JK, Heim Se, et al. Is INFUSE Bone Graft Superior to Autograft Bone? An Integrated Analysis of Clinical Trials Using the LT-CAGE Lumbar Tapered Fusion Device. *Journal of Spinal Disorders & Techniques* 2003;16(2)113-122

Cahill KS, Chi JH, et al. Prevalence, Complications, and Hospital Charges Associated With Use of Bone-Morphogenetic Proteins in Spinal Fusion Procedures. *JAMA* 2009;302(1):58-66

Jordan KP, Hayward RA, et al. Incidence of prostate, breast, lung and colorectal cancer following new consultation for musculoskeletal pain: A cohort study among UK primary care patients. *Int. J. Cancer* 2013;133:713–721

Kleeman TJ, Ahn UI, Talbot-Kleeman A. Laparoscopic Anterior Lumbar Interbody Fusion with rhBMP-2. *Spine* 2001;26:2751-2756.

Wong D, Kumar A, et al. Neurologic impairment from ectopic bone in the lumbar canal: a potential complication of off-label PLIF/TLIF use of bone morphogenetic protein-2 (BMP-2). *Spine J* 2008;8:1011-1018.