Garrison KR, Shemilt I, et al. Bone morphogenetic protein (BMP) for fracture healing in adults. Cochrane Database of Systematic Reviews 2010, Issue 6. Art. No.: CD006950

Design: Meta-analysis of randomized clinical trials and economic evaluations

Study question: Does BMP improve fracture outcomes in adults?

PICOS:

- Patient population: skeletally mature adults 16 and older with fractures, either acute or nonunion
- Interventions: BMP applied at the time of surgery for fracture treatment
- Comparisons:
    - Surgery alone
    - Surgery with or without bone graft
    - BMP plus bone substitutes versus surgery and bone substitutes
- Outcomes:
    - Primary outcomes
        - Time to union
        - Union rate without a secondary procedure for acute fractures
            - "Union" definition included bridging bone seen on radiographs
    - Secondary outcomes
        - Secondary procedures after initial surgery
        - Infection
        - Hardware failure
        - Operative parameters such as operative time and hospital stay
        - Employment status of patient
        - Time to work of patients who were working at the time of injury
        - Heterotopic bone, antibody formation, and other adverse events
    - Economic outcomes such as resource use, direct medical costs, nonmedical costs, and other measurements
- Study type: Randomized trials for clinical outcomes; economic evaluation studies for the economic outcomes

Study selection:

- Databases included MEDLINE, EMBASE, the Cochrane Register, the UK National Health Service database, and several other research registers
- Three authors independently screened titles and abstracts of articles ; two authors extracted data and assessed risk of bias
    - Risk of bias used the Cochrane Risk of Bias tool, emphasizing randomization method, allocation concealment, blinding of outcome assessment, adequate

description of inclusion criteria, accounting for dropouts, intention-to-treat analysis of primary outcomes, and comparability of baseline characteristics

- When there were multiple treatment groups in one study, the control group for that study was split proportionately and compared independently (i.e., if there were two equally large treatment groups with different doses of BMP, the control group was split in half and each half was compared with one of the treatment groups)

Results:

- The electronic search found 305 articles; 9 of these met inclusion criteria and 2 more were found by looking at reference lists, yielding 11 RCTs with 976 patients for full review
    - 4 studies investigated acute tibial fractures (2 of open tibial fractures); 4 studies investigated tibial nonunion fractures, 2 investigated critically-sized bone defects, and one investigated radial fractures
- Many studies were not well reported; only one reported the method of randomization and allocation concealment six did not report adequate descriptions of inclusion and exclusion criteria, three did not report intention-to-treat analysis and one did not report the fracture healing rate
- For time to union, 5 studies reported data; the results could not be statistically pooled, but most trials reported comparable time to healing between BMP and no BMP
- For union without secondary procedures for acute fractures, the success rate for BMP was slightly greater than without BMP (success ratio was 1.19, 95% confidence interval from 0.99 to 1.43)
    - This estimate was pooled from three studies with 481 patients; one of the studies (Govender 2002) was divided into two populations to reflect two different BMP dosages, but the total number of patients was not changed
- For achieving union in fractures with nonunion, the pooled success rate from 5 studies with 286 patients was 1.02; there was no difference in success of treating nonunion between BMP and surgery without BMP (e.g., bone graft)
- For avoiding secondary procedures after fracture surgery, fewer such procedures were done for BMP patients than for those treated without BMP (relative risk was 0.65, 95% CI from 0.50 to 0.83), with a possible dose-response trend for BMP
- Hardware failure for acute tibial fractures (screw breakage or bending) was less common with BMP than without BMP (RR was 0.64, 95% CI from 0.42 to 0.96)

Authors' conclusions:

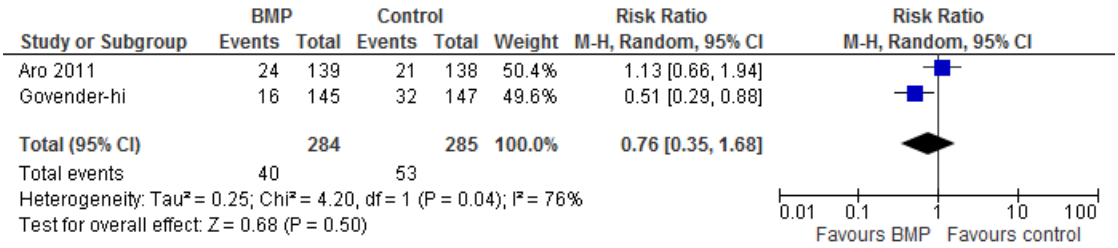
- Most studies were of poor quality; further well-designed RCTs are required to assess clinical effectiveness of BMP in treating tibial fractures
- Fracture healing without secondary procedures may occur more frequently when BMP is used at the time of surgery for acute tibial fractures

    - However, most of the data for this conclusion come from a single large study in which the BMP patients were younger than the control patients
    - Judging fracture healing radiographically is susceptible to observer variability due to the fact that judging the amount of cortical bridging requires the observer to distinguish implanted autograft from new bone; other factors also mean that some subjectivity is involved in the assessment of bone union
- There was no evidence that BMP leads to better outcomes when used to treat tibial fracture nonunion, compared to using bone graft
- Hardware failures may be less frequent with BMP in the treatment of acute tibial fractures

Comments:

- Some of the data from the largest and best-done study (Govender 2002) appears to have been estimated by calculations by the authors
    - In Analysis 1.1, for fracture union without secondary procedures, the numbers for Govender were taken from his Figure 3, which is a bar graph with percentages rather than numbers
    - In Analysis 1.4, participants requiring secondary procedure to attain union, the numbers were taken from Figure 1, which is also a bar graph with percentages rather than numbers
    - Analyses 1.1 and 1.4 are conceptually very closely related, and it is not clear why both were done
    - There is no online study protocol and the trial may not have been registered at the time it was undertaken; selective outcome reporting is possible; this is one of the criteria in the Cochrane Risk of Bias tool but is not included in the quality assessment in the Cochrane authors' methods section
- In Govender 2002, two additional sources of bias may be relevant
    - The group receiving the higher dose of BMP also had a difference in how the fracture fixation was done; 41% of the high dose BMP had reamed intramedullary nailing, versus 33% of the low dose BMP group and 27% of the no-BMP group; this is mentioned in the authors' discussions, and could favor the high dose BMP group
    - The decisions regarding secondary procedures were made by the investigators, who were aware of the initial treatment of the acute fracture; knowledge of this could have influenced the decision to undertake a secondary procedure and the level of invasiveness of that procedure when it was undertaken
        - Only 2 patients had "noninvasive" secondary procedures (ultrasound or magnetic field stimulation); both of these were in the high dose BMP group

        - The investigators' expectation that BMP would promote union could lead to delaying or deferring secondary procedures for that group
- One of the "studies awaiting assessment" on page 26 is a Wyeth trial with clinical trials registry number NCT00387686; the current clinicaltrials.gov website lists it as having been terminated by Wyeth with no further information, but has since been published by Lyon et al 2013, which found no effect of BMP in patients with closed tibial fractures treated with reamed intramedullary nailing
    - Lyon reported that only 57% of patients completed the study because of discontinuation by the sponsor
- One of the ongoing studies referenced on page 26, Cannada et al, with NCT00853489, is still recruiting patients
- Another ongoing study, Leighton et al, NCT00856479, has been withdrawn by the sponsor, but is a cost study and not a clinical effectiveness study
- A more recent study from many of the same investigators (Aro 2011) reported on some of the same outcomes as Govender 2002
    - There were low and high dose groups in Govender 2002, but a low dose group was not done with Aro 2011; pooling of outcomes therefore should be done with Aro and with the high dose group from Govender ("Govender-hi" in the forest plot)
    - Hardware failures from the two studies appear to be similar:



    - Although Aro 2011 also reported on secondary procedures with and without BMP, the rules for allowing secondary procedures in the two studies were not the same and the data should not be combined
- The timing of secondary procedures could be an important question in using it as an outcome, since a randomzed trial of reamed versus unreamed nailing (Bhandari 2008) disallowed reoperation for tibial shaft fractures for six months and reported that delaying reoperation for six months may substantially reduce the need for reoperation
- There remains insufficient information to identify subgroups which may derive greater benefit from BMP than from standard of care without BMP; for example, if fracture severity is a factor in determining the benefits of BMP, there are not yet enough patients to identify that benefit
- The Govender 2002 study is referenced twice in the forest plots, once for the low dose and once for the high dose groups; it is called "Govender 2002" both times

without identifying whether the low dose or the high dose group is being referenced, and this may be confusing

- For most of the forest plots, the low dose group is listed first and the high dose group is listed second; however, in Analysis 1.7 on page 50, this order is reversed, making it appear that hardware failure was more common in the high dose than in the low dose group, when the opposite was true
- The two dose groups in the Govender study should have been given separate identifiers in the forest plots to avoid this confusion

Assessment: Adequate meta-analysis of a largely low quality set of available studies, with current evidence not supporting measureable benefits of BMP over standard of care without BMP for tibial fractures. There is good evidence that for open tibial shaft fractures, BMP does not enhance fracture healing at 20 weeks compared to fracture fixation with intramedullary nailing.

References:

Aro HT, Govender S, et al. Recombinant human bone morphogenetic protein-2: a randomized trial in open tibial fractures treated with reamed nail fixation. J Bone Joint Surg Am. 2011 May 4;93(9):801-8.

Bhandari M, Guyatt G, et al. Randomized Trial of Reamed and Unreamed Intramedullary Nailing of Tibial Shaft Fractures. JBJS Am 2008;90:2567-78.

Govender S, Csimma C, et al. Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. JBJS Am. 2002;84:2123-34

Lyon T, Scheele W, et al. Efficacy and safety of recombinant human bone morphogenetic protein-2/calcium phosphate matrix for closed tibial diaphyseal fracture: a double-blind, randomized, controlled phase-II/III trial. JBJS Am. 2013 Dec 4;95 (23):2088-96.