**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.**

Design: Randomized clinical trial

Study question: In patients being treated for open tibial fractures with reamed nail fixation, does the addition of rh-BMP2 lead to better outcomes?

Population/sample size/setting:

- 277 patients (224 men, 53 women, mean age 38.5) treated for tibial fractures in Finland, South Africa, France, the UK, the US, Spain, and Romania
- Eligibility criteria were open tibial shaft fracture requiring statically locked intramedullary nail fixation with reaming
- Exclusion criteria (not in text of article but from study protocol at https://clinicaltrials.gov/ct2/show/NCT00161616?term=nct00161616&rank=1) were fracture distraction > 2 mm following definitive fracture fixation, purulent drainage from the fracture site or evidence of active osteomyelitis, and treatment for the fracture including further procedures to promote fracture healing prior to 16 weeks (further procedures could be done after 16 weeks as clinically indicated)

Interventions:

- All patients had initial fracture stabilization and debridement within 1 day of injury, and all patients had intramedullary nail fixation and routine soft-tissue management as standard of care (SOC)
- Randomization was to rh-BMP (BMP, n=139) or SOC alone ( n=138)
    - Randomization was stratified by the severity of the open wound as seen in the emergency room
    - BMP was administered on an absorbable bovine collagen sponge and implanted through the soft-tissue wound as an onlay bridging the fracture site

Outcomes:

- Followup was done at 6, 10, 13, 16, 20, 24, 32, 41, and 52 weeks
    - Evaluations at these time points included recording of concomitant treatments, physical examinations, lab evaluations, and tests for antibody formation to BMP or to bovine collagen
- Primary efficacy outcome was the proportion of patients with healed fractures at 13 and 20 weeks
    - Fracture was healed if there was no fracture site tenderness on manual palpation, no pain with full weight-bearing, and the presence on x-ray of

bridging callus or the disappearance of the fracture lines, no hardware failure resulting in intra-medullary dynamization or dislocation, and no secondary procedure recommended or performed to promote fracture-healing

- The planned sample size was 300 patients, but enrollment was suspended after the enrollment of 277 patients because of an observed imbalance in infection rates between treatment groups
    - There was a higher rate of adverse events requiring hospitalization (4 on the BMP group and none in the SOC group due to deep tissue infections)
    - Superficial infections were equally common between groups (15 BMP and 12 SOC), but deep infections involving bone were more common overall in the BMP group (12 BMP, 3 SOC)
- At week 13, 60% of the BMP group fractures were healed as compared to 48% of the SOC group, but this was not quite statistically significant (p=0.0541)
- At 20 weeks, there was no group difference on fracture healing (68% of the BMP group and 67% of the SOC group)
- The numbers of secondary procedures after 16 weeks was the same: 12% of the BMP group and 12% of the SOC group

Authors' conclusions:

- BMP in an absorbable collagen sponge did not significantly accelerate the healing of open tibial fractures treated with reamed intramedullary nail fixation
- An earlier study of BMP in open tibial fractures (Govender 2002) reported higher rates of reoperation and slower rates of fracture healing than the current study, but these may have been partly attributable to factors in study design
    - Reoperation in the current study was not allowed until at least 16 weeks after injury
    - The definition of fracture healing required only two cortices of the tibia rather than three as in the earlier study
    - The earlier study had more fractures of Gustilo-Anderson Type IIIA and IIIB and fewer Type I fractures; more severe fractures have higher rates of reoperation than less severe fractures
- The reasons for the higher infection rates in the BMP group than in the SOC group are not clear
    - There were fewer infections in the current study than in the 2002 study
    - In the current study, the group difference in infection rates appeared to come from the fractures of Gustilo-Anderson Type I, and may be due to the surgical procedures required to implant the collagen sponge, which could compress soft tissue and thereby compromise the blood supply to the area
- The study was single blind due to the impossibility of blinding the investigators to the study group

Comments:

- For reasons not stated, the methods section did not list inclusion and exclusion criteria, but these are available on the clincaltrials.gov website where the study protocol was registered
- The majority of patients had delayed primary closure of their fractures, which has long been a standard practice in treating open tibial fractures; however, a propensity-matched study (Jenkinson 2014), which matched primary and delayed closure of lower-trade open fractures on age, sex, severity, time to debridement, and gross contamination, reported that deep infection occurred in 3/73 fractures treated with immediate closure and in 13/73 in the matched group treated with delayed primary closure; this may be a factor to consider in future studies of treatment of open fractures
- Although the authors planned to look for whether fracture severity influenced the effect of BMP, they did not find that it made a difference; this analysis may not have had enough severe fractures to find effect modification by fracture severity
- Most of the limitations of the study are mentioned by the authors in their well-informed discussion of results

Assessment: Adequate for some evidence that in the setting of open tibial fractures treated with reamed intramedullary nailing, the use of rh-BMP at the time of fracture fixation does not measurably improve fracture healing, and may increase risks of infection

References:

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. 2002;84:2123-34

Jenkinson RJ, Kiss A, et al. Delayed Wound Closure Increases Deep-Infection Rate Associated with Lower-Grade Open Fractures. A Propensity-Matched Cohort Study. JBJS Am 2014;96:380-6.