COMMENTARY & PERSPECTIVE

Commentary on an article by Hannu T. Aro, MD, PhD, et al.: “Recombinant Human Bone Morphogenetic Protein-2: A Randomized Trial in Open Tibial Fractures Treated with Reamed Nail Fixation”

By Timothy Bhattacharyya, MD

Owing to a paucity of muscular coverage, the tibial shaft is the most common long bone to sustain an open fracture. The situation is exacerbated by the occurrence of a watershed region in the vascular supply to the tibia at the most common fracture location, the distal third of the tibia. Tibial fractures often occur in young, working men, resulting in a substantial societal impact. In 2002, the BMP-2 Evaluation in Surgery for Tibial Trauma (BESTT) investigators showed, in a randomized controlled trial, that application of a bone morphogenetic protein (BMP)-impregnated sponge resulted in a markedly lower nonunion rate¹. Unreamed nailing was primarily used in the BESTT study.

In their article, Aro et al. report the results of a randomized clinical trial in which open tibial shaft fractures treated with reamed intramedullary nailing were randomized to receive the standard of care or implantation of a recombinant human bone morphogenetic protein-2 (rhBMP-2)-impregnated collagen sponge at the fracture site. The study was halted early because a disturbing trend toward an increased rate of infection was observed in the rhBMP-2 group. The rates of healing observed at thirteen and twenty weeks and the rates of secondary procedures were statistically equivalent in the two groups.

The present study must be taken in context with the Study to Prospectively Evaluate Reamed Intramedullary Nails in Patients with Tibial Fractures (SPRINT)², in which reamed and unreamed nailing were prospectively compared. In the SPRINT, the two groups of open fractures were associated with statistically equivalent reoperation rates, but there was a trend toward better healing in the open fracture group treated with unreamed intramedullary nailing.

If reamed nailing is statistically equivalent to unreamed nailing, why did the study by Aro et al. fail to show an effect of BMP whereas the BESTT study showed marked efficacy?

The answer lies in methodological differences and our evolving understanding of tibial healing. First, the study by Aro et al. (like the SPRINT) precluded additional interventions and reoperations for the first sixteen weeks after injury, while the BESTT study did not. Second, the definition of “healing” differed among the three trials, with the BESTT study having more stringent criteria as to what constitutes a healed fracture. Because no additional interventions were allowed for the first sixteen weeks, and because the criteria for healing were less stringent, the event rate of interest (secondary procedures) declined dramatically in the study by Aro et al. compared with that in the BESTT study. As event rates decline, the power of the study declines and the need for an increased sample size increases exponentially. Thus, the chance of having a non-significant result in the trial is increased.

What then is the clinical role of rhBMP-2 in the treatment of open tibial shaft fractures? In light of the study by Aro et al., there is no role for BMP-2 in the treatment of Grade-I or II open fractures with reamed nailing because of a possible increased rate of infection, which might be a result of enlargement of the wound to insert the BMP-2 implant. There may still be a role for Grade-IIIB fractures. When used to treat Grade-IIIB fractures, the BMP-2 implant can be placed directly under the muscle that covers the bone, and the mesenchymal stem cells that form callus are recruited from the muscle. This is the likely candidate for the next prospective trial.

The BESTT investigators, SPRINT investigators, and Aro et al. have provided data that has resulted in a quantum leap in our understanding of tibial fracture-healing. Their enormous work represents an investment whose benefits, in terms of higher rates of union and lower rates of secondary operations, will be reliably reaped in the coming decade.

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perceived to influence or have the potential to influence what is written in this work. The author has not had any other relationships, or engaged in any other activities, that could be perceived to influence or have the potential to influence what is written in this work. The complete **Disclosures of Potential Conflicts of Interest** submitted by the author of this work are available with the online version of this article at jbjs.org.

References

1. Govender S, Csimma C, Genant HK, Valentin-Opran A, Amit Y, Arbel R, Aro H, Atar D, Bishay M, Börner MG, Chiron P, Choong P, Cinats J, Courtenay B, Feibel R, Geulette B, Gravel C, Haas N, Raschke M, Hammacher E, van der Velde D, Hardy P, Holt M, Josten C, Ketterl RL, Lindeque B, Lob G, Mathevon H, McCoy G, Marsh D, Miller R, Munting E, Oevre S, Nordsletten L, Patel A, Pohl A, Rennie W, Reynders P, Rommens PM, Rondia J, Rossouw WC, Daneel PJ, Ruff S, Rüter A, Santavirta S, Schildhauer TA, Gekle C, Schnettler R, Segal D, Seiler H, Snowdowne RB, Stapert J, Taglang G, Verdonk R, Vogels L, Weckbach A, Wentzensen A, Wisniewski T; BMP-2 Evaluation in Surgery for Tibial Trauma (BESTT) Study Group. Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. *J Bone Joint Surg Am.* 2002;84:2123-34.
2. Study to Prospectively Evaluate Reamed Intramedullary Nails in Patients with Tibial Fractures Investigators Bhandari M, Guyatt G, Tornetta P 3rd, Schemitsch EH, Swiontkowski M, Sanders D, Walter SD. Randomized trial of reamed and unreamed intramedullary nailing of tibial shaft fractures. *J Bone Joint Surg Am.* 2008;90:2567-78.

Update

This commentary was updated on April 15, 2011, because of a previous error. In the third paragraph, the sentence that had previously read “In the SPRINT, the two groups of open fractures were associated with statistically equivalent reoperation rates, but there was a trend toward better healing in the open fracture group treated with reamed intramedullary nailing.” now reads “In the SPRINT, the two groups of open fractures were associated with statistically equivalent reoperation rates, but there was a trend toward better healing in the open fracture group treated with unreamed intramedullary nailing.”