Bone Morphogenetic Protein and Fractures: A Meta-Analysis

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Introduction

Bone morphogenetic protein-2 and -7 are FDA-approved for use in acute open tibia fractures and nonunions, respectively. However, off-label use of these agents is common and there continues to be much debate regarding their effectiveness. The aim of this study was to systematically review, for acute fractures and nonunions, the association between BMPs and bone healing (nonunion, healing times), the need for secondary intervention, and infections.

Methods

Computerized literature databases and manual search of bibliographies were performed. Randomized controlled trials and cohort studies (retrospective and prospective) evaluating the association between BMPs and long bone healing, need for secondary intervention, and infection were included. Descriptive and quantitative data were extracted. A meta-analysis was performed using a random effects model for union, secondary intervention, and infections in BMP and non-BMP treated groups. Time to healing was evaluated using frequency-weighted means, and group weighted standard deviations. Sensitivity analyses were performed to evaluate the effects of BMP type (BMP-2 vs. 7), control group type (autograft vs. "standard-of-care"), tibia fractures, open fractures, level of evidence, and author/funding conflict of interest. Study heterogeneity, criteria of methodological quality and publication bias-adjusted for using trim and fill analysis-were also evaluated.

Results

Initial search identified 1652 references. Of the 307 articles further inspected by abstract, 19 were included (10 RCT (1,3-7,10,12,14,17), 6 prospective cohort (2,8,9,11,13,15) and 3 retrospective cohort (16,18,19). In acute fractures alone, union rates were similar for BMP-treated and non-BMP treated groups for all acute fractures, acute fractures treated with BMP-2, and acute open fractures treated with BMP-2 ($p=0.07$). Healing times were not different between the groups for acute fractures (BMP 32.2 wks vs. non-BMP 34.0 wks, $p=0.70$). In the nonunion groups, union rates were similar for BMP-treated and non-BMP treated groups ($p=0.14$); however, for the FDA-approved indication (tibial nonunions treated with BMP-7), there was a significantly higher rate of union in the BMP-treated group (OR 2.5, CI: 1.1, 6.0, $p=0.04$). For study level of evidence, there was a trend towards significance in lower level of evidence studies ($p=0.06$), compared to level 1 studies ($p=0.21$) for bony union. In level 1 studies, union rates were comparable to autograft ($p=0.07$), and there was a significantly higher rate of union ($p=0.04$) when compared to "standard of care" protocols. No difference was found in reported union rates for studies with documented conflict of interest ($p=0.42$) compared to those reporting no conflict of interest ($p=0.07$). There was a decreased overall need for secondary intervention in the BMP-treated groups for both acute fractures and nonunions ($p=0.002$). There were similar rates of infection in the BMP and non-BMP treated groups (OR 1.0, 95% CI: 0.7, 1.4, $p=0.95$). There was publication bias noted in the infection and nonunion groups, with small studies showing a larger effect size than larger studies. Trim and fill analysis was performed which resulted in similar results to the original meta-analysis.

Discussion

BMP was not found to improve union rate or healing times in any subset analysis of acute fractures. For nonunions, BMP-7 was found to have higher union rates for the FDA-approved indication compared to controls. Due to the variation in effectiveness noted in the sensitivity analyses, we would encourage further well-designed studies to identify the precise fracture population, timing, and delivery mechanism that BMP can be used to optimize bony healing.

Significance

This study provides a comprehensive review of the effects of BMP on healing of acute fractures and nonunions. Our results suggest that outcomes are highly variable according to indication, implying that more rigorous prospective studies are needed to precisely identify the fracture population, timing, and delivery mechanism that BMP can be used to optimize bony healing.

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