INPLASY

Efficacy and safety of recombinant human bone morphogenetic protein-2 biomaterials in promoting bone regeneration: a systematic review and meta-analysis

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 October 2025 and was last updated on 17 October 2025.

INTRODUCTION

Review question / Objective To systematically evaluate the efficacy and safety of recombinant human bone morphogenetic protein-2 (rhBMP-2) in promoting bone regeneration.

Condition being studied Bone defect repair has long been a major problem in orthopaedics and oral and maxillofacial surgery. Although autologous bone transplantation is regarded as the 'gold standard', it is limited by complications such as limited bone supply, pain in the bone harvesting area and infection. In recent years, bone morphogenetic protein-2 (BMP-2) has attracted clinical attention due to its potent osteogenic induction activity. Animal experiments have shown that recombinant human (rh)BMP-2 can accelerate osteoblast differentiation and promote new bone formation. In 2002, Govender et al. first demonstrated in an open tibial fracture randomised controlled trial (RCT) that rhBMP-2 can shorten healing time. Subsequently, multiple RCTs have reported positive therapeutic effects in the fields of spinal fusion, alveolar ridge preservation and cleft palate repair.

However, controversy over efficacy and safety has also emerged, with studies noting that high-dose rhBMP-2 may increase the risk of soft tissue swelling, heterotopic ossification and other complications. The effect of different carrier materials on release kinetics also leads to significant differences in efficacy. While previous systematic reviews have provided valuable insights within specific surgical indications, a broader synthesis is lacking. Many have not comprehensively accounted for the impact of critical variables such as carrier system and dosing regimen within their analyses. Furthermore, the existing body of literature lacks a unified analysis that quantifies the relative benefits of rhBMP-2 against a range of alternative treatment strategies across different clinical applications, leading to a fragmented evidence base. Furthermore, a primary challenge in synthesising the existing evidence is

the high degree of heterogeneity, likely arising from the complex interplay of multiple factors, such as patient age, anatomical site, carrier material and dosage. Traditional methods for exploring heterogeneity, such as subgroup analysis and meta-regression, are limited in their ability to model complex, non-linear interactions between these covariates. This limitation often leads to an incomplete understanding of the sources of variability in treatment effects, contributing to the inconsistent conclusions across previous reviews.

METHODS

Participant or population Study population is human patients requiring bone regeneration (e.g. for critical-sized defects, spinal fusion alveolar ridge preservation) or fracture healing (e.g. traumatic long bone fractures).

Intervention Regarding the intervention measures, the experimental group received rhBMP-2 treatment (dosage form, dose and carrier type not limited).

Comparator The control measures included autologous bone transplantation or other bone replacement materials.

Study designs to be included The PubMed, Embase, Web of Science and Scopus databases were systematically searched between the inception of each database and May 2024. The search keywords included: 'recombinant human bone morphogenetic protein-2', 'rhBMP-2', 'BMP-2', 'bone regeneration', 'bone healing', 'fracture', 'spinal fusion', 'alveolar bone' and 'randomized controlled trial', and a comprehensive search strategy was formulated by combining subject terms and free terms.

Eligibility criteria The inclusion criteria were as follows: (1) study type is RCT, no language restrictions; and (2) study population is human patients requiring bone regeneration (e.g. for critical-sized defects, spinal fusion alveolar ridge preservation) or fracture healing (e.g. traumatic long bone fractures).
The exclusion criteria included (1) non-randomised controlled studies (e.g. case series, observational studies); (2) animal studies or basic experimental studies; (3) studies without complete efficacy outcome data; and (4) studies in duplicate publication or abstract form.

Information sources Two researchers independently screened the literature, first based on the title and abstract. The full text of the studies that passed the initial screening was then screened. When disagreements occurred during the literature screening process, they were resolved through discussion involving a third-party researcher.
A standard data extraction form was used to extract the following characteristic information of each included study: basic information of the study (author, year, design type, follow-up duration); patient baseline information (age, smoking, diabetes and other comorbidities); intervention details (BMP-2 dose, carrier type, control type); and outcome indicator data (number of treatment events, number of adverse events, etc.). Following data extraction, cross-checking was performed to ensure accuracy and consistency.

Main outcome(s) The primary outcome indicators were imaging-based assessment of successful bone formation/union, measured as a bone regeneration success rate, fracture healing rate or spinal fusion rate. The secondary outcome indicator was serious adverse event (SAE) rate.

Quality assessment / Risk of bias analysis The Cochrane Collaboration's risk of bias tool (RoB 2.0, Cochrane Collaboration, Oxford, UK) was used to assess the risk of random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data and selective reporting bias. The assessment was completed by two independent assessors, and consensus was reached through discussion or third-party arbitration when the assessment was inconsistent.

Strategy of data synthesis Meta-analysis was performed using R software (version 4.4.1) and the meta package for meta-analysis. For binary outcome indicators (e.g. bone regeneration success rate), the relative risk ratio (RR) and its 95% confidence interval (95%CI) were used for combined effect size analysis. The heterogeneity evaluation used the I^2 test, with I^2>50% considered to indicate significant heterogeneity. When the heterogeneity was significant, the random-effects model was used; otherwise, the fixed-effects model was adopted. Funnel plots were created to assess the risk of publication bias.
Network meta-analysis was performed using the 'netmeta' package of R software, and different controls (autologous bone, other bone substitute materials) were included in the same analysis framework. A network evidence map was created and the efficacy was ranked (surface under the cumulative ranking curve [SUCRA] value). The random-effects model was used for the analysis, and the odds ratio (OR) and 95%CI of each node

treatment method relative to autologous bone were calculated to clarify the relative efficacy of different treatment strategies.
To explore the source of effect heterogeneity in meta-analysis, two ML algorithms, (random forest and gradient boosting) were further used to build models and analyse feature importance using Python (v3.10) and the scikit-learn library (v1.4.2) program. Features included 14 items, such as total sample size, age, dose, carrier and study site. Based on the model prediction results, the characteristic factors that contributed most to heterogeneity were determined, and further visualisation analysis was performed through the subgroup distribution of effect size.
Subgroup analysis was performed based on anatomical site (long bones, spine, maxillofacial region) and carrier type (ACS, hyaluronic acid [HA], other synthetic materials) to test the stability of the effects of different clinical scenarios and materials on the treatment effect. In terms of safety, a meta-analysis was performed for SAEs reported in the study, and the combined RR and 95%CI were calculated to evaluate the safety of rhBMP-2 intervention. Publication bias was assessed visually using funnel plots, and the possibility of publication bias was quantitatively assessed using Egger's regression test. A P value <0.05 was considered to indicate a significant risk of publication bias.

Subgroup analysis Network meta-analysis was performed using the 'netmeta' package of R software, and different controls (autologous bone, other bone substitute materials) were included in the same analysis framework. A network evidence map was created and the efficacy was ranked (surface under the cumulative ranking curve [SUCRA] value). The random-effects model was used for the analysis, and the odds ratio (OR) and 95%CI of each node treatment method relative to autologous bone were calculated to clarify the relative efficacy of different treatment strategies.
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Sensitivity analysis In terms of safety, a meta-analysis was performed for SAEs reported in the study, and the combined RR and 95%CI were calculated to evaluate the safety of rhBMP-2 intervention. Publication bias was assessed visually using funnel plots, and the possibility of publication bias was quantitatively assessed using Egger's regression test. A P value <0.05 was considered to indicate a significant risk of publication bias.

Country(ies) involved China - Tianjin Stomatological Hospital.

Keywords recombinant human bone morphogenetic protein-2; bone regeneration; systematic review; network meta-analysis; heterogeneity; machine learning; safetyrecombinant human bone morphogenetic protein-2.

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