Efficacy of autologous iliac crest bone graft and bone morphogenetic proteins for posterolateral fusion of lumbar spine: a meta-analysis of the results
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CRD summary
This review concluded that bone morphogenetic proteins were more effective than conventional autologous bone graft for posterolateral spinal fusion, but definitive conclusions could not be drawn and further research was needed. The authors' cautious conclusions seem to reflect the evidence and appear reasonable, but the above limitations should be taken into consideration when interpreting the results.

Authors' objectives
To assess the effectiveness of bone morphogenetic proteins (BMPs), compared with autologous bone graft, for posterolateral fusion of the lumbar spine.

Searching
MEDLINE/PubMed and The Cochrane Library were searched over a period of 20 years up to 2008 for articles in English. Search terms were reported. Reference lists of retrieved articles were also searched.

Study selection
Studies of adults with degenerative conditions of the lumbosacral spine requiring posterolateral fusion that compared posterolateral fusion treatment using BMP (as an enhancer or a substitute to autologous bone graft) against autologous bone graft alone were eligible for inclusion. Outcomes of interest included fusion failure, clinical failure, re-operation, operative time and hospital stay. Studies including patients with fractures of the spinal column, lumbar interbody fusions, spondylolisthesis higher than Meyerding Grade 2 and patients using regular postoperative pharmaceutical agents that could interfere with fusion were excluded from the review.

Included studies were of patients with single level degenerative disk disease and/or spondylolisthesis grade 1 or 2 (degenerative or lytic) with or without spinal stenosis. Mean ages ranged from 42.9 to 70.3 years in the treatment group and between 40.4 and 66 years in the control group. Some studies included patients with comorbidities (tobacco or alcohol use, diabetes, previous back surgery) and worker's compensation. Most studies used rhBMP-2 (20 mg or 6 mg per side), but some used rhBMP-7 (OP-1) (3.5 mg per side) using various delivery vehicles. Most studies used autogenous iliac crest bone graft as the control. Fusion failure was assessed at six, 12 and 24 to 36 months.

Two reviewers (blinded to authors and journals) independently screened studies for inclusion. Disagreements were resolved through consensus.

Assessment of study quality
Two reviewers independently assessed study quality using the PEDro scale (maximum score of 10). Criteria included assessment of: randomisation; allocation concealment; blinding of patients, therapists, or assessors; and adequate follow-up. Agreement between reviewers was assessed using the correlation coefficient for inter-rater agreement and the intraclass correlation coefficient.

Data extraction
Two reviewers extracted data to calculate relative risks on fusion failure, re-operation and clinical failure (binary outcomes) and to calculate mean differences for hospital stay and operative time (continuous outcomes), with their 95% confidence intervals (CI).

Methods of synthesis
A fixed-effect model was used to combine relative risks for binary outcomes. Weighted mean differences were pooled for continuous outcomes. A random-effects model was used where there was evidence of statistical heterogeneity. The number of patients needed to treat in order to prevent one patient experiencing a binary outcome was calculated.
Sensitivity analyses were performed to assess the robustness of the results by study design and by type of effects model used. Subgroup analyses were conducted according to type of BMP (rhBMP-2 or OP-1) and presence or absence of spinal instrumentation.

Statistical heterogeneity was assessed using the $X^2$ and $I^2$ tests. Publication bias was assessed using funnel plots

**Results of the review**

Seven trials (four quasi-randomised and two randomised controlled trials) and one prospective case-control study ($n=383$ for the seven studies) were included in the review. Sample sizes ranged from 15 to 150 patients. The mean score for study quality was 5.25, with scores ranging from 4 to 8, with good inter-rater agreement and intra-rater correlation.

**Fusion failure:** The risk of fusion failure was reduced in patients receiving BMP (14.5 per cent) compared to controls (39 per cent). Relative risk was 0.42 (95% CI: 0.28 to 0.61, $p<0.00001$; eight studies). The number needed to treat analysis indicated that four posterolateral fusion procedures with the use of autologous bone graft would result in one additional case of fusion failure.

**Time to fusion:** There was a significant reduction in risk of fusion failure with BMP compared with controls at all time points. Overall relative risk was 0.45 (95% CI: 0.35 to 0.58, $p<0.00001$; eight studies). There was evidence of statistical heterogeneity at six and 12 months.

**Re-operation, clinical failure and hospital stay:** No statistically significant differences were reported for re-operation (five studies) or clinical failure (two studies) between treatment and control groups. Hospital stay was significantly shorter in patients receiving BMP compared to controls (weighted mean difference was -1.03, 95% CI: -1.45 to -0.61, $p<0.00001$; two studies).

**Operative time:** Three of four studies reported shorter mean operative times with BMP compared to controls, but pooling of the results was not statistically significant and there was evidence of significant heterogeneity ($I^2=90.5\%$).

**Subgroup analyses:** These showed a significantly greater reduction in risk of fusion failure with BMP-2 compared with OP-1 ($p=0.003$). Studies using instrumented fusion reported significantly less risk of fusion failure in patients receiving BMP compared to controls (relative risk was 0.33, 95% CI: 0.21 to 0.52, $p<0.00001$; six studies). There was some degree of statistical heterogeneity for instrumented fusion studies. Sensitivity analyses did not significantly alter the results.

There was no evidence of statistical heterogeneity for fusion failure, re-operation, clinical failure or hospital stay. The funnel plots showed no evidence of publication bias.

**Authors' conclusions**

Bone morphogenetic proteins (rhBMP-2) appeared to be more effective than conventional autologous iliac crest bone graft for posterolateral spinal fusion and for reducing length of hospital stay. Definitive conclusions could not be drawn regarding overall clinical results, operative time and re-operations, so further well-conducted studies were needed.

**CRD commentary**

The review question and inclusion criteria were clear, although no criteria were explicitly stated for study design. The literature search involved only two electronic databases and one other appropriate source and the searches were restricted by publication date and language, which meant that language bias may have been introduced and potentially relevant papers may have been missed. Funnel plot analysis suggested no evidence of publication bias. The authors took appropriate steps to minimise the potential for reviewer error and bias. Study validity was assessed using a reliable measurement tool, although the quality of most studies was only moderate. Appropriate methods were used to combine studies and assess for statistical heterogeneity, but there appeared to be clinical and methodological heterogeneity among the studies. Included studies involved small population sizes (all studies included less than 100 patients). The authors' cautious conclusions seem to reflect the evidence and appear reasonable, but the above limitations should be taken into consideration when interpreting the results.
Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that well-designed RCTs should be undertaken to directly compare different types of BMP to identify the most effective treatment for promoting bone formation and achieving solid posterolateral spinal fusion. Further studies were needed to investigate the effect of BMP on fusion success in instrumented and non-instrumented posterolateral procedures.

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