Osteoinductive bone graft substitutes for lumbar fusion: a systematic review

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CRD summary
The authors concluded that recombinant human bone morphogenetic protein-2 may be an effective alternative to autologous iliac crest bone graft in lumbar fusion. Data about other bone graft substitutes were limited. There were limitations in reporting of review methods, but overall the authors’ cautious conclusions appeared to reflect the evidence from a small number of studies of apparently limited quality.

Authors' objectives
To compare the efficacy and safety of osteoinductive bone graft substitutes versus allografts and autografts in patients who underwent lumbar fusion.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials were searched from inception to April 2009 for peer-reviewed studies published in English. Search terms were reported.

Study selection
Controlled trials were eligible if they evaluated osteoinductive bone graft substitutes in adults who underwent lumbar fusion with anterior lumbar interbody fusion, posterolateral lumbar fusion or posterior lumbar interbody fusion. Studies had to evaluate at least one of non-union (primary outcome, defined as failure to fuse on computed tomography scan or radiographs), Oswestry low-back pain disability questionnaire (or Oswestry disability index), operating time, blood loss and length of stay. The review also assessed adverse events.

Most of the included studies evaluated recombinant human bone morphogenetic proteins (rhBMP-2 or rhBMP-7); other studies evaluated demineralised bone matrix, activated or autologous growth factor or platelet gel. Bone morphogenetic proteins were combined with various osteoconductive materials in about half of the studies and with allografts, autografts and pedicle screw instrumentation in other studies. In most studies (all except two) the comparison intervention was autologous iliac crest bone graft (AIBG); one study used a local autograft and one study used a femoral ring allograft as the control intervention.

All patients had lumbar or lumbosacral fusion for lumbar degenerative joint disease. In most studies patients underwent posterior lumbar interbody fusion; in other studies patients underwent anterior lumbar interbody fusion and less commonly anterior-posterior lumbar fusion.

The authors did not state many reviewers performed study selection.

Assessment of study quality
The validity of randomised controlled trials (RCTs) was assessed using the five-point Jadad score of randomisation, blinding and withdrawals.

The authors did not state how many reviewers assessed validity.

Data extraction
Numbers of patients with dichotomous outcomes of interest were extracted and used to calculate relative risks (RRs) with 95% confidence intervals (CI) after discounting for losses to follow-up.

Data were extracted by one reviewer and checked by a second reviewer.

Methods of synthesis
Where possible, data from homogeneous RCTs were pooled using a fixed-effect Mantel-Haenszel model to calculate relative risks and 95% CIs. The number needed to treat (NNT) and 95% CI was calculated for non-union. Heterogeneity was assessed using the Q statistic and I². Where pooling was not possible, studies were combined in a narrative synthesis.

The possibility of publication bias was explored using a funnel plot and Begg’s and Egger’s tests. The trim-and-fill method was used to adjust for any publication bias.

**Results of the review**

Seventeen studies were included (n=1,342 patients): nine RCTs (n=692), five prospective controlled studies (n=357) and three retrospective controlled studies (n=293). Sample size ranged from 14 to 279. In most studies follow-up was 24 months (range 12 to 48 months). In one RCT, the surgeon and patients was blinded to the intervention. In eight RCTs, the assessor of radiographic fusion was blinded. Six studies reported losses to follow-up. Jadad scores ranged from 1 to 3 out of a possible 5.

**Radiographic non-union (RCTs only):** RhBMP-2 was associated with a statistically significant reduction in risk of nonunion compared to autologous iliac crest bone graft at 12 to 24 months (RR 0.27, 95% CI 0.16 to 0.46, NNT=8, 95% CI 5 to 12; six RCTs). No significant heterogeneity was found. Similar results were found when studies were grouped by type of fusion.

RhBMP-2 plus collagen plus an interbody fusion cage was associated with a statistically significant reduction in risk of nonunion compared to autologous iliac crest bone graft plus a cage in patients who underwent anterior lumbar interbody fusion (RR 0.43, 95% CI 0.19 to 1.00; two RCTs). No significant heterogeneity was found.

Two RCTs that compared RhBMP-2 plus compression resistant matrix plus pedicle screw instrumentation with autologous iliac crest bone graft plus pedicle screw instrumentation in patients who underwent posterolateral lumbar fusion reported a significant reduction in non-union in rhBMP-2 groups; there was significant heterogeneity I²=51%.

There was no significant difference in risk of non-union between rhBMP-7 and autologous iliac crest bone graft or local autograft (three RCTs).

**Secondary outcomes (RCTs):** RhBMP-2 was associated with a significant reduction in operating time compared to autologous iliac crest bone graft in four out of five RCTs, a significant decrease in blood loss in two out of five RCTs and a significant decrease in length of stay in one out of five RCTs. There was no significant difference between rhBMP-2 and autologous iliac crest bone graft in the likelihood of improvement on the Oswestry Disability Index (four RCTs)

**Adverse events:** The authors stated that none of the adverse events appeared to be associated with the study intervention. Pain at the graft site was commonly reported for autologous iliac crest bone graft.

The funnel plot for the effect of rhBMP-2 on nonunion showed evidence of publication bias; results for Begg’s and Egger’s tests were conflicting.

Results were reported for interventions evaluated in individual studies and non randomised studies.

**Authors' conclusions**

Recombinant human bone morphogenetic protein-2 may be an effective alternative to autologous iliac crest bone graft in lumbar fusion. Data about other bone graft substitutes were limited.

**CRD commentary**

The review question was clearly stated. Inclusion criteria were defined appropriately. Several relevant sources were searched. No attempts were made to minimise publication and language biases. Methods were used to minimise reviewer errors and bias during data extraction; it was unclear whether similar steps were taken in study selection and validity assessment. The validity of RCTs was assessed and results were reported. The authors stated that the RCTs
were of moderate quality, but assessment and reporting of validity were limited and analyses were not based on intention-to-treat data. Pooling only data from RCTs was appropriate. Heterogeneity was assessed. Some limitations of the review were discussed.

There were limitations in reporting of review methods, but overall the authors’ cautious conclusions appeared to reflect the evidence from a small number of studies of apparently limited quality.

**Implications of the review for practice and research**

**Practice:** The authors stated that recombinant human bone morphogenetic protein-2 may be an effective alternative to autologous iliac crest bone graft in lumbar fusion.

**Research:** The authors stated that adequately powered RCTs were required to evaluate rhBMP-2 and assess clinically relevant outcomes. Future studies should evaluate the efficacy of demineralised bone matrix or activated/autologous growth factor for lumbar fusion.

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