Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review

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Executive summary

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Objectives

The objectives of this study were to assess the clinical effectiveness and cost-effectiveness of bone morphogenetic protein (BMP) for the treatment of spinal fusions and the healing of fractures compared with the current standards of care.

Methods

Electronic literature databases, related journals and references from identified studies were searched for relevant studies in January 2006, then an updated search was performed only for randomised controlled trials (RCTs) in November 2006. The searches were not restricted by language, publication status or date. Due to the anticipated paucity of relevant studies, all studies that reported on BMP for treatment of spinal fusion or fracture were included. However, in our analyses, we focused on evidence from RCTs because of the poor quality of data from identified case series. All data were extracted by one reviewer and checked by another.

Models developed by ABACUS International were modified or updated to evaluate the cost-effectiveness of BMP for open tibial fractures and spinal fusion.

Results

Quantity and quality of included RCTs

Eight randomised trials of BMP for tibial fractures, one for scaphoid non-union and 12 randomised trials of BMP for spinal fusion were included. These trials had several methodological weaknesses, including unreported randomisation and allocation methods, incomparable baseline characteristics between the groups, failure to perform intention-to-treat analysis or to use independent blinded assessors and failure to report reasons for drop-outs. Some secondary outcomes were not measured and/or reported. Because of insufficient sample size in most trials, patient baseline comparability between trial arms was not achieved and the statistical power to detect a moderate effect was low.

Effectiveness of BMP for tibial fractures

According to the data from three trials (494 patients in total), the use of BMP increased fracture union among patients with acute tibial fractures [pooled odds ratio (OR) 1.65, 95% confidence interval (CI) 1.12 to 2.45]. This pooled analysis was dominated by the data from a large trial (n = 450). Data from the largest trial (n = 450) also indicated that high-dose BMP (1.5 mg/ml) is more effective than a lower dose (0.75 mg/ml) for open tibial fractures. Four small trials (245 patients in total) found that the healing rate in the BMP group was not statistically significantly different from that in the autogenous bone grafting group for patients with tibial non-union fractures (pooled OR for union rate 0.82, 95% CI 0.25 to 2.64). The use of BMP reduced the number of secondary interventions in patients with acute tibial fractures compared with controls.

Effectiveness of BMP for scaphoid non-union

Only one small RCT (n = 18) was identified. Very limited evidence indicated that BMP in scaphoid non-union was safe and may help to accelerate non-union healing when used in conjunction with either autograft or allograft.

Effectiveness of BMP for spinal fusion

Evidence from seven trials (n = 631 in total) showed that BMP-2 is more effective than autogenous bone graft for radiographic fusion in patients with single-level degenerative disc disease (pooled OR 3.87, 95% CI 1.74 to 8.59). Two small trials (n = 56 in total) compared BMP-7 and autograft for degenerative spondylolisthesis with spinal stenosis and found no statistically significant difference (pooled OR 0.87, 95% CI 0.15 to 5.08). No statistically significant difference was observed in one small trial (n = 20) that compared BMP-7 and autograft spondylolysis (pooled OR 0.38, 95% CI 0.05 to 2.77). The use of BMP was associated with an average of 25-minute reduction (95% CI 11 to 37 minutes) in operating time and a shorter hospital stay (0.75 days, 95% CI 0.31 to 1.19 days) compared with autograft. BMP may be associated with improvement in clinical outcomes such as Oswestry Disability Index score, SF-36 score and back and leg pain. The proportion of secondary interventions tended to be lower in the BMP group.
than that in the control group, but the difference was not statistically significant (pooled OR 0.62, 95% CI 0.28 to 1.39). Data from trials on time to return to work postoperatively were sometimes difficult to interpret because of unclear or inappropriate methods used for data analysis and results presentation.

Cost-effectiveness assessments
The incremental cost of BMP for open tibial fractures is estimated to be about £3.5 million per year in the UK. The estimated incremental cost per quality-adjusted life-year (QALY) gained was £32,603, with a wide 95% CI from £14,085 to £61,257. The probability that cost per QALY gained is less than £30,000 for open tibial fracture was 35.5%. The cost-effectiveness ratio is sensitive to the price of BMP and the severity of open tibial fractures.

The use of rhBMP for spinal fusion surgery may increase the cost to the UK NHS by about £1.3 million per year. The estimated incremental cost per QALY gained was about £120,390. The probability that BMP is cost-effective (i.e. that the cost/QALY is less than £30,000) was only 6.4%. We re-analysed data on time to return to work after spinal surgery, and revealed that patients in the BMP group were not returning to work earlier than those in the control group. From the societal perspective, the estimated total cost of using BMP for spinal fusion is about £4.2 million per year in the UK.

Conclusions
Additional BMP treatment plus conventional interventions is more effective than the conventional intervention alone for union of acute open tibial fractures. The cost-effectiveness of additional BMP may be improved if the price of BMP is reduced or BMP is mainly used in severe cases.

The use of BMP may eliminate the need for autogenous bone grafting so that costs and complications related to harvesting autograft can be avoided. In non-unions, there is no evidence that BMP is more or less effective than bone graft; however, it is currently used when bone graft and other treatments have failed.

The use of BMP-2 in spinal fusion surgery seems more effective than autogenous bone graft in terms of radiographic spinal fusion among patients with single-level degenerative disc disease. There is a lack of evidence about the effectiveness of BMP for other spinal disorders including spondylolisthesis and spinal stenosis. There was limited evidence showing that BMP is associated with greater improvement in clinical outcomes such as Oswestry Disability Index score, SF-36 score and back and leg pain. According to the results of economic evaluation, the use of BMP for spinal fusion is unlikely to be cost-effective.

Recommendations for further research
The following areas are recommended for further research:
- clinical trials of BMP that include formal economic evaluation
- a multicentre RCT covering fracture non-union
- a multicentre RCT covering interbody and/or posterolateral spinal fusion
- RCTs covering non-tibial acute long bone fractures
- RCTs comparing BMP-2, BMP-7 and controls.

Publication
The Health Technology Assessment (HTA) programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Secondly, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Thirdly, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer-reviewed by a number of independent expert referees before publication in the widely read monograph series *Health Technology Assessment*.

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Reports are published in the HTA monograph series if (1) they have resulted from work for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned by the HTA Programme as project number 04/34/02. The contractual start date was in November 2005. The draft report began editorial review in August 2006 and was accepted for publication in March 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

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