Bone morphogenetic proteins in the non-healing of fractures and spinal fusion

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

Health Technology Assessment 2007; Vol. 11: No. 30

Health Technology Assessment
NHS R&D HTA Programme
www.hta.ac.uk

Executive summary

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

Garrison KR, Donell S, Ryder J, Shemilt I, Mugford M, Harvey I, *et al.* Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review. *Health Technol Assess* 2007;**11**(30).

NIHR Health Technology Assessment Programme

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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.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.