Cost effectiveness of tibial nonunion treatment: a comparison between rhBMP-7 and autologous bone graft in two Italian centres

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Record Status
This is an economic evaluation that meets the criteria for inclusion on NHS EED.

CRD summary
The study aimed to capture the costs and assess the cost-effectiveness of recombinant human bone morphogenetic protein 7 (rhBMP-7, eptotermin alpha) and autologous bone grafting (ABG) for treating tibial non-union. The authors concluded that rhBMP-7 was more cost-effective than ABG, but that more evidence was desirable. The economic evaluation was limited by its retrospective design, small sample, inadequate control for confounders and short time horizon. The validity of the study results is unclear.

Type of economic evaluation
Cost-effectiveness analysis, cost-utility analysis

Study objective
The study aimed to capture the costs and assess the cost-effectiveness of recombinant human bone morphogenetic protein 7 (rhBMP-7, eptotermin alpha) and autologous bone grafting (ABG) for treating tibial non-union.

Interventions
RhBMP-7 was compared with ABG (standard care). RhBMP-7 was used as an osteoinductive agent. ABG was used for its osteopromotive and osteoinductive properties.

Location/setting
Italy/secondary care.

Methods
Analytical approach:
The economic evaluation was based on a small observational study (54 patients) conducted in two Italian centres during 2010 to 2011. There were two economic evaluations: a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA). Both analyses were conducted from the perspective of the Italian health system and presented incremental cost-effectiveness ratios (ICERs) as their output. The cost utility analysis was conducted on a subset of 30 patients.

Effectiveness data:
A small retrospective observational study was conducted in two Italian orthopaedic referral hospitals. Archives of the two hospitals were screened to identify patients who underwent surgery for non-tibial union using rhBMP-7 or ABG between 1997 and 2009. Patients were included in the study if they were diagnosed with a post-traumatic tibial non-union (defined as the failure to progress to a union after at least nine months and after at least one unsuccessful surgery); and sufficient follow-up data (defined as follow-up until confirmed success or 12 months). The primary measure of effectiveness was the rate of successful union after surgery. Secondary outcomes included time to union and perceived quality of life. Adverse events were measured.

Monetary benefit and utility valuations:
Utility scores were derived from a subset of 30 patients in one study centre using EQ-5D values elicited from the patients. These values were taken at time of data collection (2010 to 2011). Patients were asked for their perceived quality of life at one, six, and 12 months follow-up after surgery. Utility scores at the different follow-ups were assumed to last for 1.5 months for one month follow-up, five months for six month follow-up, and five and a half months for the 12-month follow-up.
The primary measure of benefit in the CEA was successful tibial reunions. The measure of benefit in the CUA was quality-adjusted life-years (QALYs).

Cost data:
The cost data were collected for all in-patient and out-patient direct costs from the initial tibial injury until the end of follow-up. Direct medical costs categories included out-patient visits, hospitalisations, surgery costs, physiotherapy and diagnostics. These cost categories included personnel costs, device costs, room costs, depreciation and consumables. Information on drugs used and blood units administered was available. Most costs were derived from individual data in the study centres; diagnostic costs were derived from a regional administrative database. All costs were reported in 2009 Euros (EUR). An additional analysis was conducted comparing costs to hospital reimbursements. Reimbursements were calculated using regional diagnosis-related group (DRG) values matched to the codes in the patient discharge registries.

Analysis of uncertainty:
Differences in baseline characteristics and outcomes were assessed for statistical significance. A probability of 0.05 or less was considered statistically significant. Sensitivity of the results to alternative cost values was tested.

Results
No statistically significant differences were found between the two study groups at baseline. Twenty non-unions were treated successfully using ABG (76.9% success) and 25 were resolved using rhBMP-7 (89.3% success); the difference was not statistically significant ($p=0.22$). Among successful cases, the rhBMP-7 group showed shorter mean times to clinical and radiological union; these differences were not statistically significant ($p=0.23$ and $p=0.25$). Statistically significant differences were found in intra-operative bleeding, perioperative and late onset adverse events in favour of rhBMP-7 ($p<0.007$).

The mean cost to successfully resolve a tibial non-union was EUR 9,965.42 for ABG and EUR 9,476.45 for rhBMP-7, a difference of EUR 488.96 per successful resolution of tibial non-union favouring rhBMP-7. The CUA found that mean (0.022 difference) and median (0.08 difference) differences in utility score favoured rhBMP-7 over the first year after surgery, this resulted in ICERs between EUR 9,730 per QALY for median scores and EUR 35,637 per QALY for mean scores.

The reimbursement analysis showed that the two hospitals performing tibial non-union surgeries sustained financial losses for performing both procedures and losses were greater for rhBMP-7.

Authors' conclusions
The authors concluded that rhBMP-7 was more cost-effective than ABG, but that more evidence was desirable to decrease uncertainty around the estimates.

CRD commentary
Interventions:
Neither intervention was described beyond stating the mechanism of action. It was unclear what was involved in the treatments. The authors indicated that rhBMP-7 had been compared with the use of platelet-rich plasma in tibial non-unions, but platelet-rich plasma was not included as a comparator.

Effectiveness/benefits:
The effectiveness evidence was derived from a very small observational sample of patients. It did not appear that any methods were used to control for potential confounding factors. There were few statistically significant differences in baseline data but it appeared that some potential confounders favoured rhBMP-7: severity tended to be lower in rhBMP-7; there was a tendency towards anatomical alignment in rhBMP-7; there appeared to be differences in Weber and Cech group; and there appeared to be more and larger size bone defects in the ABG group. The presence of confounders all acting against ABG potentially biased the economic evaluation. It appeared that utility scores were measured long after the surgeries took place. This gave potential for inaccurate recall. It was unclear whether the utility scores were valid. No baseline measurement was taken for utility scores and this may have led to confounding. Ideally, baseline utility differences should be controlled for in an analysis. Utility scores were assumed to apply to an amount of time for each follow-up; no justifications were provided for this set of assumptions. The current set of assumptions gave equal time in each utility score to ABG and rhBMP-7; this implicitly assumed that the pattern of recovery was
similar between the two treatments and this was not supported by the study evidence. The reported utility scores were all given as median and interquartile range, mean utility scores were not reported for any time point. Table 9 was inconsistent with the outcomes reported in the text (ABG was reported to have higher median and mean overall utility than rhBMP-7 in Table 9).

Costs:
Costs were derived from appropriate sources and were generally well reported. It appeared that relevant costs were included in the analysis. The analysis of cost differences was subject to the same potential biases as the analysis of effect differences.

Analysis and results:
Overall, the study results should be viewed with caution as there was no control for potential confounders, the very small study size and because the methods used surrounding the utility analysis were of unclear validity. In addition to these limitations, study follow-up was limited and the time horizon of the economic evaluation was limited to one year. As described by the authors, tibial non-union is a chronic condition with significant long-term affects on quality of life. The short time horizon may underestimate the costs and benefits of treatment. Sensitivity analysis was limited to testing a couple extreme assumptions. As acknowledged by the authors, reducing uncertainty would be desirable. An appropriate discussion of other studies in the field, and some discussion of study limitations, were reported.

Concluding remarks:
The economic evaluation was limited by its retrospective design, small sample, inadequate control for confounders and short time horizon. The validity of the study results is unclear.

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