

Considered Judgement Form

This form is a checklist of issues that may be considered by the Purchasing Guidance Advisory Group when making purchasing recommendations.

Meeting date: 7th June 2006

Topic: A review of the efficacy of Bone Morphogenetic Proteins (BMP) in spinal fusion

Background and Purpose:

Hitherto the standard treatment to achieve fusion of vertebrae involved grafting of bone, often harvested from the patient's iliac crest; a procedure associated with pain and other morbidities. An alternative is a bone graft from a donor, but then there are risks of disease transmission. The potential advantage of BMP is that bone grafts become unnecessary. BMP is a growth factor that induces formation of bone at the site of implantation. BMP were originally developed to treat fracture of long bones that had failed to heal. Their use was later extended to spinal surgery. The complex anatomy of the spine and associated neural elements presents unique challenges to combine biomaterials and surgical technique. To exemplify, the surgeon may approach the spine from the anterior or posterior aspect, use a variety of instrumentations to immobilise and in some instances perform laparoscopic surgery, he/she then has a choice of implants to deliver the BMP. Patients also vary in presentation and some may require revision surgery due to failed previous treatment. The efficacies of each these procedures have not been thoroughly investigated. However the majority of claims to ACC involve fusion of lumbar vertebrae with the spine approached posterior laterally. This approach has been used in several clinical trials. At present there are two main products on the market that incorporate either BMP-2 or BMP-7. With regard to ACC claimants, only BMP-2 has been used in spinal fusion. The commercial products are sold as InductOs™ or INFUSE® Bone Graft.

The literature review produced by the EBH team on BMP and spinal fusion has been sent to two orthopaedic surgeons. They were asked to assess completeness of coverage of the literature, accuracy of interpretations and comment from a clinician's perspective. To date one referee has replied and their comments are presented in appendix 1.

1. Effectiveness, Volume of Evidence, Applicability /Generalisability and Consistency

Comment here on the extent to which the service/product/ procedure achieves the desired outcomes. Specific reference needs to be made to safety. Report number needed to treat and harm where possible, 1 any issues concerning the quantity of evidence and its methodological quality and the extent to which the evidence is directly applicable or generalisable to the New Zealand Population, and the degree of consistency demonstrated by the available evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence

Clinical trials of BMP are constrained by the inability to (a) include a placebo and (b) blind patients and surgeons to treatment. This affects subjective outcomes like assessment of pain, although measures of bone fusion can be impartially assessed by a radiologist who does not know the treatment. Overall the evidence that BMP achieve desired outcomes, ie comparable to grafting bone from the iliac crest, is convincing. We identified ten studies (4 randomised controlled trials and 6 case series) in which patients received only BMP and in all these studies there was a degree of successful bone fusion. These papers form the body of evidence. The strongest evidence comes from a single well-designed randomised control trial which has been reviewed by regulatory authorities in the US, European Union and Australia. In this pivotal trial patients were randomised to receive either iliac crest bone graft or rhBMP-2. The evidence showed that BMP was equally effective as bone graft. Several papers report on pain and include the Oswestry index of disability (the Oswestry questionnaire is appended to the literature review). There is not strong evidence that long term pain relief is better using BMP compared to autograft. Estimates of short-term pain relief

<p>could be clouded by pain from the donor site.</p> <p>Regulatory authorities have issued several contra-indications to using BMP and these are itemised in the report. For example, one concern is that antibodies may form to BMP and thus if a woman becomes pregnant those antibodies could cross the placenta and affect foetal development.</p> <p>Several health insurance companies have issued their own guidelines on payments for treatments that include BMP. These guidelines are similar to those produced by the US FDA</p> <p>In January 2006 Medsafe confirmed that the commercial products incorporating human recombinant BMP have not been approved in New Zealand for spinal fusion.</p>
<p>2. Cost</p> <p>Comment on any economic costs associated with this service, product or procedure</p>
<p>There are about 30 ACC codes relating to surgical procedures on the spine. Information on costs of these procedures in relation to bone fusions has not been extracted from ACC. One important comparison is the cost of using BMP compared to costs involved in harvesting bone grafts. Correspondence in Dec 2003 with the manufacturer of INFUSE® Bone Graft gave costs of NZ\$5000-7000 depending on size and an additional NZ\$5600 for titanium cages if these are used in the procedure.</p>
<p>3. Clinical impact</p> <p>Comment on the clinical impact e.g. size of population, magnitude of effect, relative benefit over other management options, resource implications, balance of risk and benefit.</p>
<p>Enquiries from Healthwise Specialist Services and the Elective Surgery Unit in Dunedin yielded the following preliminary information which may be relevant. This information has not been checked and could be incomplete. In 2004 and 2005 ACC paid for 1108 and 1015 lumbar discectomies with 366 and 364 lumbar fusions respectively. The complete list of spinal procedures is given in Appendix 2 and a cursory look indicates about 500 procedures per year may involve some form of bone fusion. In contrast, a request for information on the use of BMP yielded the following information; in 2004 there were 29 core and 10 non-core procedures in which BMP-2 was used and in 2005 14 and 5 (the 2005 data may be incomplete) Appendix 3.</p>
<p>4. Equity, Maori Health, Pacific Health, Acceptability</p> <p>Comment on the extent to which the service, product or procedure reduces disparities in health status (equity of access, resources, health outcome), is consistent with the treaty of Waitangi and encourages Maori/ Pacific participation in providing and using service, product and procedures, and is consistent with values and expectations of New Zealanders.</p>
<p>BMP incorporated into commercial products is produced from a cell line into which the human gene has been inserted. It therefore arises from genetic modification and some prospective patients may find that unacceptable.</p>
<p>5. Possible Purchasing Options</p> <p>List the possible purchasing options.</p>
<p>These considerations relate <u>only to spinal fusion</u> and do not embrace other treatments e.g. long bone fracture or dental.</p> <ol style="list-style-type: none"> 1. Not to purchase if bone graft is feasible, this denies a reasonable choice to patient 2. Not to purchase if contraindicated e.g. pregnant or likely to become pregnant, skeletally immature, allergic to bovine collagen, tumour at site. 3. Purchase only if provider has been trained, or has access to expertise, in using BMP and related devices. Could mitigate failure rate 4. Purchase in accordance with guidelines (FDA, Blue Cross/Blue Shield etc). Criteria include previous failed bone graft or inadequate donor tissue other risks factors for poor take of bone grafts include smoking osteoporosis and diabetes. 5. Purchase on a case by case basis with appropriate outcome assessment

6. Evidence Statement

Summarise the advisory group's synthesis of evidence relating to this service, product or procedure, taking the above factors into account, and indicate the evidence level that applies.

There is sufficient evidence to support the use of BMP-2 in lumbar fusion. There is no evidence of benefit for the use of BMP – 2 or 7 for thoracic and cervical fusions, and there may be potential for rare but serious side effects. Patients and surgeons should be informed of the contra-indications that exist.

7. Purchasing Recommendations

What recommendation(s) does the advisory group draw from this evidence?

To purchase with agreed conditions to be negotiated with NZ Orthopaedic Association Spinal Subgroup; that guideline to be specific to BMP2 and lumbar spinal fusion.