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Horizon Scanning Technology Prioritising Summary

INFUSE® bone graft for the treatment of open tibial fractures

February 2005
(Updated March 2006)



ASERNIP'S

**Australian
Safety
and Efficacy
Register
of New
Interventional
Procedures -
Surgical**



**Royal Australasian
College of Surgeons**



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The production of this Horizon scanning prioritising summary was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

This Horizon scanning prioritising summary was prepared by staff from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).

**Name of Technology:**

INFUSE® bone graft for the treatment of open tibial fractures.

Purpose and Target Group:

The INFUSE® device consists of an absorbable bovine collagen sponge soaked in recombinant human bone morphogenetic protein-2 (rhBMP-2). Used in conjunction with an internal stabilisation device, the INFUSE® device can induce bone growth at the site of implantation. It may therefore be applicable for the treatment of delayed union or non-union tibial fractures.

Stage of Development (in Australia):

- Experimental
- Investigational
- Nearly established
- Established
- Established but changed indication or modification of technique
- Should be taken out of use

The INFUSE® bone graft is registered in the Australian Register of Therapeutic Goods (ARTG number: 121164)

International Utilisation:

COUNTRY	LEVEL OF USE		
	Trials underway	Limited use	Widely Diffused
United States		✓	

Impact Summary:***Background***

The tibia is fractured more frequently than any other long bone in the human body (<http://www.emedicine.com>). Fractures of the tibia and fibula can occur anywhere along the length of the bones. Fractures may be open (compound) or closed (simple), displaced or undisplaced, and angulated or not angulated, stable or unstable (<http://www.emedicine.com>).

Treatment of tibial fractures requires alignment and stabilisation of the fracture until arthrodesis can occur. Depending on the type of fracture, treatment may involve conservative plaster fixation or operative reduction and rigid internal fixation. Internal fixation includes the use of screws, wires, pins or plates. Atrophic non-unions require augmentation to stimulate bone formation. This may require bone grafting, soft tissue coverage, or other forms of biologic stimulation, such as bone morphogenetic proteins



(BMPs) (<http://www.emedicine.com>). The treatment of open tibial fractures is often complicated by delayed union and non-union (Govender *et al.* 2002).

INFUSE® bone graft is an absorbable collagen sponge soaked in recombinant human bone morphogenetic protein-2 (rhBMP-2). The collagen sponge allows delivery of rhBMP-2 to the fractured area. Used in conjunction with a stabilisation device, INFUSE® promotes bone formation and hence arthrodesis (<http://www.medtronic.com>). However, the use of INFUSE® is contraindicated for patients with a known hypersensitivity to rhBMP-2, bovine Type 1 collagen or other components of the formulation. INFUSE® should not be used in the vicinity of a resected, extant tumour or in patients with any active malignancy or undergoing treatment for malignancy. It should not be implanted in skeletally immature patients, patients with an inadequate neurovascular status (e.g. high risk of amputation or compartment syndrome) or patients who have an active infection at the operative site. Furthermore, the INFUSE® should not be used in pregnant women, as the effects of rhBMP-2 on the foetus have not been evaluated (<http://www.fda.gov/cdrh/pdf4/p000054a.pdf>).

Clinical Need and Burden of Disease

The epidemiological impact of disorders that result from long-bone delayed union or non-union in Australia is currently unknown. However, the incidence of tibial non-union is estimated to range from 2% to 10% of all tibial fractures, with the incidence increasing for high-energy injuries and open fractures (<http://www.emedicine.com>). The prevalence of delayed union has been reported to range between 16% and 60% for less severe fractures (Gustillo-Anderson types I, II, and IIIA) and from 43% to 100% for more severe fractures (Gustillo-Anderson types IIIB and IIIC) (Govender *et al.* 2002). Patients are often disabled to some degree, a consequence of which tends to be an increase in obesity. This impacts not only on the immediate well-being of the patient, but also contributes to an increase in the incidence of cardiovascular disease and diabetes, which impacts heavily on employment through diminished productivity and medical costs.

Estimated Speed, Geographic and Practitioner Use Patterns of Diffusion in the Health System

One randomised controlled trial has reported the use of the INFUSE® bone graft device to treat 450 patients with open tibial fractures since April 1997 (Govender *et al.* 2002). Approval by the FDA for the use of INFUSE® bone grafts to treat open tibial fractures was granted on April 30, 2004 (<http://www.fda.gov/cdrh/pdf4/p000054a.pdf>). However, numerous publications exist for INFUSE® bone grafts in the treatment of various spinal disorders (5 randomised controlled trials, 1 costing study, 2 case series) and dental procedures (3 case series).

Existing Comparators

- Autogenous bone graft



- Allogeneic bone graft
- OP-1 putty
- Fusion by synthetic implant

Estimated Cost Impact

The costs associated with this new product are not available. The cost of surgery involving autogenous or allograft bones in Australia is also not available. However, reimbursement fees as stated by the Medicare Benefits Schedule for bone grafts to the tibia are \$469.90 or \$602.45 with internal fixation (Item numbers 48206 and 48209). Reimbursement for the harvesting of grafts (autogenous) is \$117.40 for a small quantity, \$195.65 for a large quantity and \$313.00 for vascularised pedicle (Item numbers 47726, 47729 & 47732). According to the HIC, for the 2003/2004 financial year there were 458 claims to Medicare for bone grafts to the tibia and 211 with accompanying internal fixation (<http://www.hic.gov.au>).

Efficacy and Safety Issues

List of Studies Found	Total	Tibial
Total number of studies	12	1
Randomised controlled trials	6	1
Non-randomised comparative studies	1	-
Case series studies	5	-

The studies included in this summary are highlighted in bold in the reference list.

Safety and efficacy data from one randomised controlled trial has been selected for inclusion in this summary. The included randomised controlled trial was the only study found to evaluate the use of INFUSE® bone graft on tibial fractures.

The randomised controlled trial conducted by Govender *et al.* (2002) evaluated the standard of care (intramedullary nail fixation and routine soft-tissue management) to standard of care and an implant (absorbable collagen sponge) containing 0.75 mg/mL or 1.5 mg/mL of rhBMP-2. Patients in the 1.5 mg/mL rhBMP-2 group had a 44% reduction in the risk of failure compared to standard care (i.e. secondary intervention due to delayed union; relative risk 0.56, 95% confidence interval 0.40 to 0.78). Patients requiring secondary intervention were 38/145 (26%), 54/145 (37%) and 68/147 (46%) in the 1.5 mg/mL, 0.75 mg/mL and control group respectively ($p=0.0004$). Fracture healing was observed in 50% of the patients at 184, 187 and 145 days in the control, 0.75 mg/ml and 1.50 mg/mL rhBMP-2 groups respectively.

The adverse events reported were leg pain, oedema, infection, knee and ankle pain and hardware failure (screw breakage or bending). There was no overall difference in the rate of fracture site infection across treatment groups; however, in the subset of patients with the most severe wounds, the rate of infection was decreased in patients who received 1.5



mg/mL rhBMP-2. Thirty two of 147 patients in the control group (22%) had hardware failure compared with 16/145 (11%) in the 1.5 mg/mL rhBMP-2 group. Patients with overall pain were lower in the rhBMP-2 implant groups (67% and 68% in 0.75 mg/mL and 1.5 mg/mL respectively) compared to the control group (79%). Antibodies to rhBMP-2 was reported in 1/147 (1%), 3/145 (2%) and 9/145 (6%) of patients in 0.75 mg/mL, 1.5 mg/mL and control groups respectively. Antibodies to type-1 bovine collagen developed in 60 patients: 9/147 (6%), 22/145 (15%) and 29/145 (20%) of patients in the control, 0.75 mg/mL and 1.5 mg/mL groups respectively. One patient died in each of the three groups, none of the deaths were considered to be related to study treatment.

There is limited evidence for the safety and efficacy of INFUSE® bone graft. The study conducted has indicated that the procedure may promote bone growth and hence arthrodesis of tibial fractures.

2006 update

A search of relevant databases, online journals and the internet was conducted in February 2006, following the recommendation in February 2005 that INFUSE® bone graft for tibial fractures be monitored for assessment in 12 months time. No new evidence on the safety and efficacy of this technique on treating tibial fractures was retrieved.

Based on the limited evidence available, it is recommended that this procedure be archived.

Ethical Issues

No issues were identified from the retrieved material.

Cultural or Religious Considerations

The collagen used in the absorbable sponge is manufactured bovine bone collagen. This may be an issue for some cultural or religious groups.

Other Issues

Vegetarians may also have issues with the bovine derived bone collagen.

Recommendation:

Limited evidence exists on the safety and efficacy of INFUSE® bone grafts for the treatment of tibial fractures. Long-term safety and efficacy data with large patient numbers will be required before this device can be widely accepted. Evaluation of INFUSE® bone grafts for tibial fractures revealed that the device is also used for a range of other indications, such as spinal fusion and in dental procedures. It is recommended that INFUSE® bone graft for the treatment of all indications be assessed.



- Horizon Scanning Report Full Health Technology Assessment
- Monitor Archive

However, it should be noted that the UK NHS has commissioned a report on bone morphogenetic proteins for patients with fractures or needing spinal fusion (04/34).

References:

Govender S, Csimma C, Genant HK, Valentin-Opran A. Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures. *Journal of Bone and Joint Surgery* 2002; 84(12):2123-34.

Sources of Further Information:

Ackerman SJ, Malifios MS, Polly DW. Economic evaluation of bone morphogenetic protein versus autogenous iliac crest bone graft in single-level anterior lumbar fusion: and evidence-based modelling approach. *Spine* 2002; 27(16):S94-9.

Baskin DS, Ryan P, Sonntag V, Westmark R, Widmayer MA. A prospective, randomised, controlled cervical fusion study utilising recombinant human bone morphogenetic protein-2 with the Cornerstone-SR allograft ring and the Atlantis anterior cervical plate. *Spine* 2003; 28(12):1219-25.

Boyne PJ, Marx RE, Nevins M, Triplett G, Lazaro E, Lilly LC, Alder M, Nummikoski P. A feasibility study evaluating rhBMP-2/absorbable collagen sponge for maxillary sinus floor augmentation. *International Journal of Periodontics Restorative Dentistry* 1997; 17(1):11-25.

Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with taper interbody cages. *Journal of Spinal Disorder Technology* 2002; 15(5); 337-49.

Burkus JK, Transfeldt EE, Kitchel SH, Watkins RG, Balderston RA. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. *Spine* 2002; 27(21):2396-408.

Burkus JK, Dorchak JD, Sanders DL. Radiographic assessment of interbody fusion using recombinant human bone morphogenetic protein type 2. *Spine* 2003; 28(4): 372-7.

Burkus JK, Heim SE, Gornet MF, Zdeblick TA. Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-cage lumbar tapered device. *Journal of Spinal Disorder Technologies* 2003; 16(2):113-22.



Cochran DL, Jones AA, Lilly LC, Fiorellini JP, Howell H. Evaluation of recombinant human bone morphogenetic protein for oral applications including the use of endosseous implants: 3-year results of a pilot study in humans. *Journal of Periodontology* 2000; 71(8):1241-57.

Geiger M, Li RH, Friess W. Collagen sponges for bone regeneration with rhBMP-2. *Advances in Drug Delivery Review* 2003; 55(12):1613-29.

Haid RW, Branch CL, Alexander JT, Burkus JK. Posterior lumbar interbody fusion using recombinant human morphogenetic protein type 2 with cylindrical interbody cages. *Spine Journal* 2004; 4(5):527-38.

Howell TH, Fiorellini J, Jones A, Alder M, Nummikoski P, Lazaro M, Cochran D. A feasibility study evaluating rhBMP-2/absorbable collagen sponge device for local alveolar ridge preservation or augmentation. *International Journal of Periodontics Restorative Dentistry* 1997; 17(2):124-39.

Lanman TH, Hopkins TJ. Early findings in a pilot study of anterior cervical interbody fusion in which recombinant human bone morphogenetic protein-2 was used with poly (L-lactide-co-D,L-lactide) bioabsorbable implants. *Neurosurgical Focus* 2004; 16(3):E6.

Lanman TH, Hopkins TJ. Lumbar interbody fusion after treatment with recombinant human bone morphogenetic protein-2 added to poly(L-lactide-co-D,L-lactide) bioresorbable implants. *Neurosurgical Focus* 2004; 16(3):E9.

Polly DW, Ackerman SJ, Shafferty CI, Ogilvie JW, Wang JC, Stralka SW, Mafilios MS, Heim SE, Sandhu HS. A cost analysis of bone morphogenetic protein versus autogenous iliac crest bone graft in single-level anterior lumbar fusion. *Orthopedics* 2003; 26(10):1027-37.

Search Criteria:

A search of MEDLINE, PubMed and Cochrane Library, Current Controlled Trials metaRegister, UK National Research Register, International Network for Agencies for Health Technology Assessments, relevant online journals and the Internet was conducted in September 2004.

Search terms used were: 'absorbable collagen sponge', 'INFUSE bone graft', 'infuse and bone', 'absorbable collagen sponge and tibia' and 'rhBMP-2 and sponge and tibia'.

This Horizon Scanning Prioritising Summary was prepared by Ms Lynette Cufone from the NET-S Project, ASERNIP-S for the Health Policy Advisory Committee on Technology (Health PACT), on behalf of the Medical Services Advisory Committee (MSAC) and the Australian Health Ministers' Advisory Council (AHMAC).