Heterotopic ossification after the use of commercially available recombinant human bone morphogenetic proteins in four patients

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Recombinant bone morphogenetic proteins (rhBMPs) are present in two commercially available osteo-inductive composite materials currently available for use in the management of the healing of fractures. Infuse (Medtronic Sofamor Danek Inc., Minneapolis, Minnesota) is rhBMP-2 and is used in the treatment of acute open tibial fractures as well as in anterior single-level lumbar vertebral-body spinal fusion, osteogenic protein 1 (OP-1) (Stryker Biotech, Hopkinton, Massachusetts) is rhBMP-7 and has shown efficacy in the treatment of recalcitrant nonunions of long bones, posterior lumbar fusion, and, more recently, in the healing of nonunion of the pelvis. The potential benefits of using these rhBMPs include a decrease in post-operative pain and donor-site morbidity associated with the harvesting of autografts and a reduction of costs associated with the treatment of delayed and nonunion. In a large prospective, randomised trial, Govender et al. used rhBMP-2 for the treatment of open tibial fractures. They noted accelerated repair of the fracture and a reduction in infection in type-III open fractures without an increase in complications when compared with treatment by placebo. These benefits were confirmed in a later report which included an additional 60 patients. Others have also shown benefits in patients with no reported adverse effects.

The use of rhBMPs to augment bone formation has been described in applications including the healing of nonunion, distraction osteogenesis, osteotomy, peri-prosthetic reconstruction, free fibular grafting and joint arthrodesis. A theoretical inherent risk with their use is the formation of ectopic bone due to diffusion into adjacent soft tissues. These recombinant proteins have been in clinical use for approximately five years and as yet only a few adverse effects have been described in the literature, these include post-operative swelling in the cervical spine and heterotopic ossification (HO) of the triceps. We report the occurrence of substantial HO after the use of Infuse and OP-1 in the treatment of acute fractures and delayed union in four patients.

Case reports
Details of the four patients are given in Table 1.

Case 1. A 54-year-old obese woman who fell 25 feet without loss of consciousness sustained an LC2 pelvic fracture according to Gustillo and Anderson, a comminuted sacral fracture, a grade-II, open supracondylar fracture of the left humerus (Fig. 1a), bilateral pulmonary contusions and a left-sided pneumothorax. She was haemodynamically stabilised and a left-sided chest drain was inserted, she was intubated, sedated and transferred to the operating theatre where the left elbow wound was debrided and a spanning external fixator was applied for initial stabilisation of the fracture. She was returned to the operating theatre 11 days later for closed reduction and percutaneous fixation of the sacral fracture. On the 22nd day after the injury definitive internal fixation of the distal humeral fracture was undertaken. The elbow was approached posteriorly for fixation of the medial and lateral columns. After reduction, a gap, which remained medially was filled with fresh autograft consisting of fracture callus and new bone initially debrided from the site of the fracture. Although the risk of nonunion in distal humeral fractures is
thought to be low\textsuperscript{16} the loss of bone, the open nature of the injury, and the multiple surgical procedures may have placed her at a higher risk of nonunion. Therefore the graft was augmented with Infuse BMP-2 on an absorbable collagen sponge placed along the anteromedial, anterolateral and direct anterior borders of the distal humerus. Postoperative rehabilitation included serial static splinting which gradually increased the degree of extension. At seven weeks radiographs showed adequate formation of callus and maintenance of reduction (Fig. 1b), with some HO predominantly posteriorly (Fig. 1c). At five months after injury, she presented with an acute decrease in range of movement and with the elbow fixed at 90°. Radiographs showed bridging HO from the olecranon to the distal humerus which extended posteriorly into the fascial planes (Fig. 1d). She underwent excision of HO with capsular release and manipulation under anaesthesia. After anterior and posterior debridement and capsulorrhaphy, she regained full flexion and loss of 5° of extension, but at three weeks after operation was found to have medial dislocation of the ulna and radius. Subsequently, she underwent open reduction with placement of a transfixion screw through the olecranon into the distal humerus. After four weeks, the transfixion screw was removed and the passive range of movement was from 30° to 120°. At the most recent follow-up (6 months), the range of movement had decreased to 30° to 100°. Radiographs showed no recurrent HO and stable reduction of the elbow (Fig. 1e).

Case 2. A 55-year-old man sustained a fracture of the left humeral shaft with no other significant injuries. Initial fixation of the fracture was undertaken with a locked intramedullary nail. Radiographs at 16 months showed a nonunion (Fig. 2a) and he underwent removal of the intramedullary nail, debridement of the nonunion and lateral plating of the humerus with placement of an OP-1/thrombin pouch. This consisted of placing OP-1 at the site of the fracture followed by adding thrombin slowly over several minutes to augment healing (Fig. 2b). Healing progressed with resolution of pain but at ten weeks after operation he complained of discomfort and swelling of the arm. Radiographs showed HO of the soft tissues lateral to the plate. At two years the lesion was shown to be stable and he was asymptomatic. At 26 months after revision plating (Fig. 2c), he underwent hemiarthroplasty of the ipsilateral shoulder for worsening shoulder pain and degenerative joint disease. The upper aspect of the HO was resected to allow removal of the proximal screw and placement of the prosthesis. Since this time he has been free from symptoms.

Case 3. A 61-year-old woman with multiple medical problems including coronary artery disease sustained a fracture of the right humeral shaft in a fall. The fracture was initially treated with an intramedullary nail. One year later there was nonunion and fixation was augmented by synthetic demineralised bone matrix, this was done at an outside facility.

<table>
<thead>
<tr>
<th>Case</th>
<th>Location</th>
<th>AO classification</th>
<th>Open/grade</th>
<th>Reason for use</th>
<th>BMP type used</th>
<th>Thrombin pouch</th>
<th>Brooker classification of HO</th>
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<tr>
<td>1</td>
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<td>Infuse</td>
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<td>IV</td>
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<td>No</td>
<td>Nonunion</td>
<td>OP-1</td>
<td>Yes</td>
<td>III</td>
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<tr>
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<td>A1</td>
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<td>OP-1</td>
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<td>IV</td>
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<tr>
<td>4</td>
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<td>OP-1</td>
<td>Yes</td>
<td>III</td>
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</table>

Table I. Comparison of the four cases with regard to the type of injury, commercial bone morphogenetic protein (BMP) used, and the extent of heterotopic ossification (HO)

Radiographs of a 54-year-old woman with multiple injuries, including a grade-II open supracondylar fracture of the left humerus showing a) the initial injury, b) after fixation and treatment by autograft supplemented with BMP-2, c) at ten weeks after operation with evidence of heterotopic ossification, d) heterotopic ossification bridging the elbow posteriorly and extending into the fascial planes five months after injury and e) after excision of heterotopic ossification with stable reduction of the elbow.
Two years after the injury (Fig. 3a), there remained a symptomatic nonunion. The nail was removed and double plating of the humeral shaft was carried out, augmented by an OP-1/thrombin pouch. At six weeks after the operation she complained of pain and acute limitation of movement from 70° to 90°. Radiographs showed massive diffuse formation of HO from the surgical neck of the humerus extending down to the anterior aspect of the elbow along the course of brachialis (Fig. 3b). She underwent exploration and excision of the calcified brachialis which was found to be the cause of the restricted movement. The radiological appearance of the new bone was diffuse in nature and lacked the sharp borders seen in the more prevalent types of HO which form as a result of enchondral ossification.17 The images were more characteristic of intramembranous bone function, similar to that seen in progressive osseous heteroplasia,18-20 although no histological examination was undertaken to confirm this observation. At follow-up at one year she remained asymptomatic with a full range of movement.

Case 4. A 20-year-old woman sustained a grade-II open,8 AO type C-2 fracture21 of the distal humerus which was initially treated by irrigation, debridement, primary closure, and application of a cast. Radiographs, one week later, showed some intra-articular displacement (Figs 4a and 4b) and open reduction and internal fixation was performed (Fig. 4c). The site of the fracture was irrigated before and after fixation and an OP-1/thrombin pouch was placed adjacent to the area of comminution. At follow-up at two months there was limited movement, from 35° to 100°. Radiographs showed some ectopic ossification anterior to the trochlea and posteriorly at the tip of the olecranon (Fig. 4d). He returned at 18 months with pain and limitation of movement and there was a mature area of HO anteriorly and posteriorly, incongruent with the olecranon (Fig. 4e). She underwent excision of the posterior HO with improvement in the range of movement and relief from pain.
Discussion

HO can occur in many sites. While the mechanisms associated with many cases of HO remain elusive, one hypothesis is that it is associated with an inflammatory response resulting from the elaboration of specific biochemical mediators and growth factors, which leads to the recruitment of mesenchymal stem cells capable of differentiating into cartilage and/or bones. The role of an inflammatory response as a contributing factor in the development of HO can be inferred from the apparent prophylactic effects of indometacin in the prevention of HO around the pelvis after hip surgery, acetabular fracture, and in the spine after injury to the spinal cord. Other anti-inflammatory agents have also been shown to be effective in the prevention of HO after hip replacement.

Some authors have, however, recently questioned the use of indometacin as prophylaxis after acetabular fractures. There are several trauma-related situations in which HO is known to occur. Myositis ossificans can develop secondary to an intramuscular haematoma. The bone typically forms through endochondral ossification. This begins with inflammation and includes oedema and cellular infiltration. As formation progresses, proliferation of fibroblasts and deposition of osteoid occur. The rim is preferentially ossified and is replaced by lamellar bone as the HO reaches maturation. Pelvic fractures which are treated through a posterior approach are also subject to high rates of HO. It is possible that systemic factors play a role in these situations, possibly related to genetic predisposition based on human leukocyte antigens. Susceptible patients may express or release factors which can initiate the formation of new bone at these sites. Patients with cerebral trauma are susceptible to HO, and systemic levels of basic fibroblast growth factor have been shown to be elevated in these instances. Eid et al found that serum from polytraumatised patients significantly inhibited apoptosis in human mesenchymal bone-marrow cells, further implicating a systemic factor in the enhancement of HO.

HO of the elbow may occur after burns and dislocation but is uncommon after operative management of intra-articular fracture of the distal humerus. The rate of HO after injury to the elbow has been reported to be between 0% and 14%, but these studies included cases of dislocation and head injury, neither of which occurred in any of our patients. In a review of intra-articular distal humeral fractures over a period of five years, Helfet and Schmeling found an incidence of only 4% for all degrees of HO. The formation of HO in our cases was related to the force of the injury and specifically to fracture dislocations. The degree of soft-tissue injury has been correlated with the formation of HO in distal humeral fractures and may have played a role in the patient treated with BMP-2 in our series. Kundel et al noted that HO usually occurred anteriorly. The diffuse nature of the new bone formation, particularly on the posterior aspect of the elbow (cases 1 and 4), also suggests an effect of growth-factor supplementation.

As previously stated, inflammation associated with the bone and soft-tissue trauma may have provided the chemotactic stimulus for the recruitment of the necessary mesenchymal precursor cells. It has been proposed that BMP4 is involved in the extensive endochondral ossification seen in fibrodysplasia ossificans progressiva. The transfer of the gene for BMP2 into skeletal muscle has been shown to promote both endochondral and intramembranous ossification. Expression of BMP2 and BMP7 have also been shown to induce BMP4 expression. The addition of rhBMPs may then have provided the osteoinductive stimulus for chondro-osteogenic differentiation leading to the development of HO in these cases.
Until now there has been only one published report of HO and the use of rhBMPs in treatment of fractures. Wysocki and Cohen describes HO in a fracture at the elbow treated with OP-1. The patient had nonunion of the distal humerus and a history of smoking which may have had a contributing role, although the intramuscular location of the new bone formation was not typical.

There have been at least two reports of complications from the use of Infuse in the cervical spine.14,52 Shields et al published a retrospective review of 151 patients who had undergone anterior cervical fusion supplemented by high doses (up to 2.1 mg per level) of Infuse. Complications were reported in 23.2% of patients and included 15 (9.9%) haematomas and two cases of paralysis of the vocal cords and Horner Syndrome, but these findings had undergone anterior cervical fusion supplemented by Wysocki and Cohen described HO in a fracture at the pseudarthrosis with or without bone formation in the lung.

HO can result in substantial morbidity, particularly when it occurs around a joint, which in our series required additional surgery. Our cases suggest the possibility of a cause-and-effect relationship between the development of HO and the use of rhBMP in skeletal reconstruction. In order to test this hypothesis, a sufficiently powered prospective clinical study is required.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References


