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Use of bone morphogenetic proteins in arthrodesis: Clinical results

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ABSTRACT

Bone grafting is not routinely required in primary arthrodesis in the absence of infection, avascular necrosis, bone defect or previous non-union; when any of the above factors is present, autograft is the gold-standard method. However, donor site morbidity and the quantitative and qualitative limitations of autograft have led to the development of alternatives. This study documents the use of the bone morphogenetic protein BMP-7 in a total of 19 joint fusions (ankle, subtalar, talonavicular, pubic and sacroiliac). Healing rates of 90% and satisfactory subjective functional outcome in 70% of cases were recorded over a minimum follow-up of 15 months. These data should provide a sound foundation for future clinical trials evaluating the application of BMP-7 in the fusion of joints.

Introduction

Arthrodesis was widely practised before the era of arthroplasties and the contemporary advances in the management of intraarticular fractures and osseo-cartilaginous pathology. Currently arthrodesis still represents the ultimate in spine and pelvic girdle surgery, is a reliable method of surgical management of the small joints of the extremities and, for the large joints of the upper and lower extremities, is a salvage or last-resort option.[1,14,27,33–35,44,53]

The existing methods of achieving a successful arthrodesis vary according to the anatomical site, the underlying pathology, the presence or absence of previous implants, and the condition of the surrounding soft-tissue envelope. The basic principles are, however, the same and consist of debridement of the articular cartilage, preservation of adequate bone stock and stable compressive fixation in a position that permits optimal function of the fused extremity.[23,38–41,44]

Bone grafting is used as an osteoinductive and osteogenic stimulus in cases of suboptimal local or systemic biology, in failed attempted fusions and revisions and in the presence of large defects after debridement requiring an active void filler. The different grafting options described in the literature include autologous bone graft from the pelvis or adjacent anatomical sites, allografts, bone substitutes or their combinations.[42,43,52]

Bone morphogenic proteins (BMPs) emerged during the past 15 years and, since recombinant technology achieved their biosynthesis, have been applied and have proved their potency as osteoinductive agents in cases of acute fracture,[29,50] long-bone non-union[9,18,32] and spinal fusion.[26,36] Of these proteins, currently BMP-2 and BMP-7 are commercially available, and ample evidence has been collected during the past decade regarding their approved indications[3,4,9,15,21,28] and their off-licence use.[8,11,18–20,29,48] Different authors have described the application of these BMPs in achieving a successful arthrodesis in different anatomical sites,[19,20] extrapolating the experience gained from the spinal fusions.

In this study we present our experience over a period of 4 years with the administration of BMPs to a series of people undergoing arthrodesis of the appendicular skeleton or fusion of the pelvic girdle joints.

Materials and methods

A prospectively created database of the BMP-7 applications at our institution was used to identify cases of arthrodesis. The existing database includes demographics, previous medical history, comorbidities, intraoperative and in-hospital details of each person and also data expanding to the whole follow-up period until successful bone healing and discharge of the person from the outpatient clinic.

The indications for arthrodesis were posttraumatic arthritis and chronic pain, chronic postpartum pelvic girdle pain and septic destructive arthritis. The indications for the off-licence BMP-7 application at the surgeon's discretion included previous failed attempts (nine cases) and the presence of risk factors for impaired bone healing such as tobacco use, diabetes mellitus, chronic corticosteroid therapy and poor local biology.

All the cases included in the study were treated with local application of BMP-7 (OP-1®, Osigraft®; Stryker-Biotech, Hopkinton, MA), a combination of 3.5 mg rhBMP-7 with 1 g purified type I bovine collagen as a carrier. The product is reconstituted with saline to form a paste, which is then implanted at the fusion site. BMP-7 was used as a substitute for autologous bone graft in eight cases. In the other 11 cases, where the defect was greater than 2 cm, BMP-7 was used in conjunction with autologous bone grafting or allograft.

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Table 1
Case series of fusions of foot, ankle or pelvic joints over a period of 4 years

Clinical details	Arthrodesis					
	Pubic symphysis	Sacroiliac	Subtalar	Talonavicular	Ankle	Total
Number of cases	8	4	3	1	3	19
Men/women	1/7	1/3	3/0	0/1	2/1	7/12
Mean age in years (range)	37.8 (28–65)	42.5 (28–56)	37.3 (31–42)	42	39 (29–59)	37.8 (28–65)
BMP-7 alone	2	2	3	1	-	8/19
BMP-7 and autograft	6	2	-	-	-	8/19
BMP-7 and allograft	-	-	-	-	3	3/19
Fusion failure	1	1	-	-	-	2/19
Mean months to clinical fusion (range)	4.7 (4–6)	4 (4–6)	3.7 (3–4)	3	3.7 (3–4)	4.2 (3–6)
Mean months to radiological fusion (range)	6.6 (5–9)	4 (4–6)	5.3 (4–6)	4	5–7 (5–6)	5.7 (4–9)
Subjective outcome	2 excellent, 3 good, 1 fair, 2 poor	1 excellent, 2 good, 1 poor	1 excellent, 1 good, 1 fair	1 excellent	1 excellent, 1 good, 1 fair	6 excellent, 7 good, 3 fair, 3 poor

BMP-7, bone morphogenetic protein-7 /OP-1®.

Accomplishment of both clinical and radiological union was considered a successful outcome. Clinical union was defined as pain-free full weight bearing needing no further surgical intervention, and radiological union was defined as evidence of new bone bridging the fused joint on more than one radiological view.

At the final follow-up, participants were asked to express their subjective opinion of their outcome according to a simple scale consisting of four levels: excellent, good, fair and poor. The minimum duration of follow-up was 15 months.

Results

Between May 2005 and May 2008, 19 anatomical sites in 16 cases where BMP-7 was applied on the indication of joint fusion of the pelvis or the appendicular skeleton, were identified (Table 1). The majority of cases involved severe posttraumatic arthritis in nine people and ten anatomical sites: three ankle, three subtalar, one talonavicular, two pubic symphysis and one sacroiliac. Six women had chronic postpartum pelvic girdle pain and underwent, in all, six pubic symphysis and two sacroiliac joint fusions; and one person was treated for chronic septic destructive sacroiliatis.

Standard surgical approaches and methods of open reduction, debridement and plate fixation were used in all cases (Figs. 1–3). The postoperative rehabilitation and mobilisation scheme involved, in cases of pelvic fusion, a minimum non-weight-bearing period of 2 months and wheelchair transfer. In all cases full weight bearing was allowed when radiological progress in healing was evident.

The median follow-up period was 30.4 months (range 15–51 months). All attempted fusions healed in a median period of 6 months (range 4–9 months), with some variations related to the anatomical site and, in one case, to incomplete fusion of the pubic symphysis and left sacroiliac joint. In the latter, a case of posttraumatic pelvic fracture, symptoms persisted and neither fusion healed. Further autologous grafting with BMP-7 application was required, as well as a revision of the osteosynthesis 1 year after the initial BMP-7 procedure (Table 1). No secondary surgical interventions were necessary in the remaining 15 cases, and no postoperative complications were related to BMP-7 use. Three superficial wound infections were managed with oral antibiotics; one deep vein thrombosis of an ankle fusion was verified with duplex ultrasound, and warfarin was administered for 4 months without any secondary sequel.

At the last follow-up appointment, the majority of the participants were satisfied with the outcome and the function of their affected limb or pelvis. Two people (three anatomical sites) reported poor outcome and related their dissatisfaction to the persistency of pelvic girdle symptoms. One of these was the man whose arthrodesis did not heal, and the other was a woman who remains wheelchair bound, although with no sign of local or systemic infection or implant loosening and with radiological evidence of a healed pubic symphysis fusion. She received a diagnosis of fibromyalgia and is currently being attended by clinical psychiatrists and the pain management team, almost 3 years after her operation.

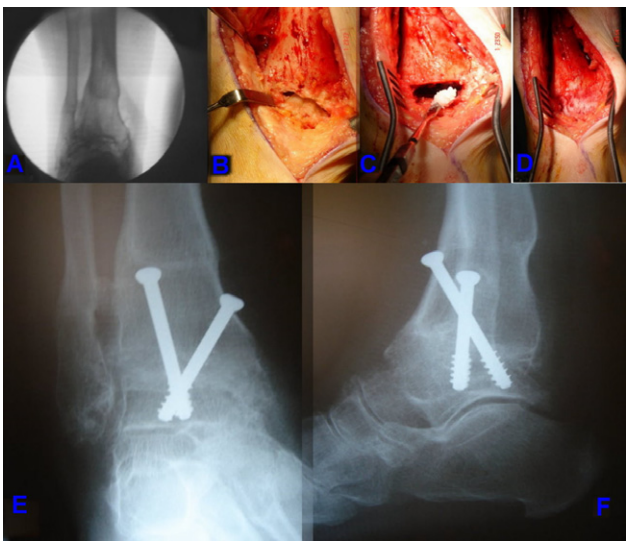

Fig. 1. Woman 59 years old, diabetic, with posttraumatic malunion of right pilon fracture, severe ankle arthritis and equinus deformity. (A) Intraoperative image intensifier anteroposterior radiographic view at time of arthrodesis. (B) Diminished joint space of right ankle, and malunion of pilon fracture. (C) After debridement of distal tibia and talus, application of bone morphogenetic protein (BMP-7 / OP-1®). (D) After application of the BMP-7 at fusion site. (E) Six months from arthrodesis, anteroposterior radiograph showing radiological union, with 'good' subjective clinical outcome. (F) Six months from arthrodesis, lateral radiograph showing radiological union, with subjective report of 'good' outcome.

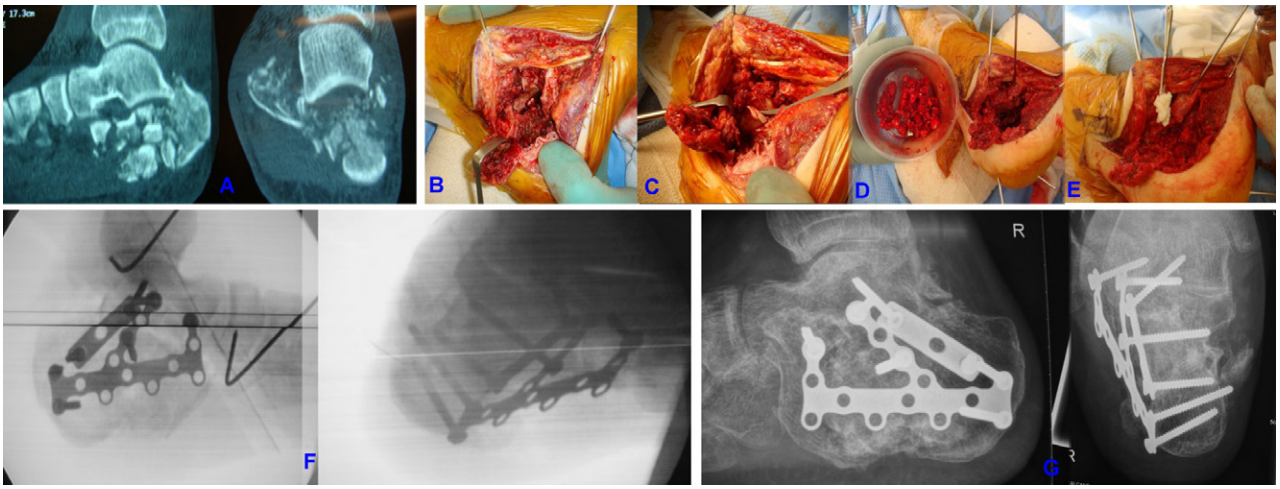

Fig. 2. Man 31 years old, heavy smoker, after falling 10 feet, with comminuted fracture of the right calcaneus, primary subtalar fusion. (A) Sagittal and coronal reconstruction computed tomography of right calcaneal fracture. (B) Surgical approach illustrating elevation of lateral calcaneal wall with comminution and created void. (C) Resection of articular cartilage of subtalar joint. (D) Re-implantation of cancellous bone fragments to void and subtalar arthrodesis site. (E) Application of bone morphogenetic protein (BMP-7 / OP-1®) putty combined with cancellous bony fragments, comprising grafting composite. (F) Intraoperative image intensifier radiographic views (lateral and axial) of subtalar arthrodesis and osteosynthesis. (G) Radiological union 4 months after surgery.

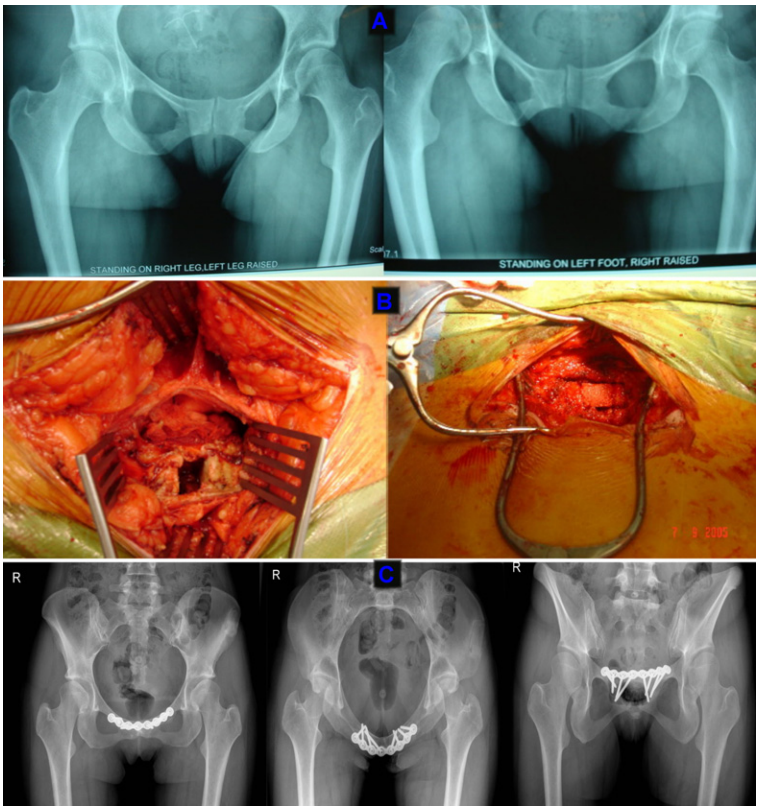

Fig. 3. Woman 36 years old, with postpartum pelvic instability and chronic pelvic pain. (A) Preoperative stork views of pelvis with evidence of chronic pelvic ring instability and degenerative changes to pubic symphysis joint. (B) Intraoperative photographs of pubic symphysis, after debridement and application of autologous structural graft in combination with bone morphogenetic protein (BMP-7 / OP-1®). (C) Six months postoperatively, anteroposterior and inlet-outlet radiographs of pelvis showing complete radiological healing of fused pubic symphysis.

Discussion

Arthrodesis as an operative treatment for large or smaller joints of the extremities remains a viable option, despite the development of arthroplasty for most joints in the appendicular skeleton. Either as a salvage procedure or as first-line treatment, arthrodesis offers in most cases pain-free weight bearing and correction of deformities.[1,7,16,25,33,39,44,45] With regard to the three joints of the pelvic girdle, fusion represents the most reliable solution in those cases where severe instability, arthritis and persistent pain are present. Careful exclusion of lumbar referral pain and other extraarticular pathology is recommended before proceeding to a fusion of the pubic symphysis or the sacroiliac joints. To our knowledge, no comparative studies of successful fusion rates or clinical outcomes exist for the various arthrodesis techniques. Reports of small, retrospective series reveal generally positive results (healing rates over 85%).[14,19,30,51] Nevertheless, pain relief

is rarely total in these cases and postoperative recovery may be prolonged and incomplete.

Bone grafting as part of an arthrodesis procedure has been described and used regularly during the past century, and is generally considered an important component of foot and ankle arthrodesis if the potential for union is compromised by factors such as infection, avascular necrosis, bone defects and previous non-union.[24,31,37,46] Bone grafting is not routinely required in primary arthrodesis in the absence of these complicating factors.[46] The gold standard in all bone grafting indications has been autologous bone graft[43] which, in most of the reported clinical series,[23,42] has involved cancellous bone from the iliac crest and/or from the proximal or distal tibial metaphysis; small bone plugs from the calcaneal tuberosity; small bone debris from osteophyte or lateral malleolus excision or from the drilling of subchondral bone; or corticocancellous bone from the iliac crest or proximal tibial metaphysis. The reported efficacy of autologous bone grafting in the different arthrodesis sites varies with the authors, indications, underlying pathology and method of fixation. Recent systematic reviews of foot and ankle surgery report a successful union of 72% to 100%;[22–24] for the pelvic girdle joints evidence is comparatively scarce.[10,19,30] The considerable rates of associated complications and morbidity of the donor sites[2,12,54] (donor site pain, haematoma, infection, injury to the lateral femoral cutaneous or gluteal nerves or to the superior gluteal artery, pelvic or tibial fractures, hernias through the iliac defect, gait disturbances and iliac vein thrombosis with resulting pulmonary embolism), the prolonged anaesthesia, the inherent limitations in quantity and quality of bone, and the associated costs have led the scientific community to develop and test other biological enhancing agents.[5,6]

Osteoconductive materials and allografts have proved quite effective in the treatment of lower extremity cystic lesions, fractures and arthrodesis. They are considered comparable to conventional autogenous iliac crest grafts in terms of direct medical costs (diminished anaesthesia time, theatre costs and hospital stay).[42] However, these applications are considered solely space fillers, and are used mostly in the presence of large defects at the arthrodesis sites. Some reports concern the use of demineralised bone matrix (DBM),[47] indicated most often in 'difficult' cases of impaired biology or deficient adjacent cancellous bone, or in revisions of failed cases. The evidence regarding this application of DBM lacks of adequate strength.[13,23,42] Treatment with BMPs, currently the most potent osteoinductive agents,[52] has been documented in sporadic reports or small, uncontrolled series.[17,19] However, the evidence of their effectiveness and safety is geometrically increasing since their initial discovery,[49] resulting in the approval of two of them (rhBMP-7and rhBMP-2) by the US Food and Drug Administration for clinical applications.[8,15,21] These agents have been used off-licence in foot and ankle arthrodesis surgery in both Europe[19,20] and the USA.[17]

To date there are no peer-reviewed publications comparing the safety, efficacy and costs of these alternative options to grafting in the clinical setting of joint fusions other than the spine. To the best of our knowledge the present study represents the first case series focusing on the use of BMPs, in particular BMP-7, in the clinical setting of arthrodesis of the foot, ankle or pelvic girdle. We acknowledge the low level of evidence of this uncontrolled case series. Nevertheless, the 90% healing rates of the fused joints as well as the functional results, which compare well with the standard methods of arthrodesis with/without autograft, provide a sound foundation for future clinical trials.

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