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The use of bone morphogenic protein-7 (OP-1) in the management of resistant non-unions in the upper and lower limb

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ABSTRACT

The aim of the present study was to investigate the safety and efficacy of local implantation of BMP-7 for the treatment of resistant non-unions in the upper and lower limb. Fifty-two patients (30 males, mean age 52.8 years; range 20–81) were treated with local BMP-7 implantation in a bovine bone-derived collagen paste with or without revision of fixation. Thirty-six patients had closed injuries, ten had open injuries and six had infected non-unions. Patients had undergone a mean of 2 (1–5) operations prior to implantation of BMP-7. Clinical and radiological union was achieved in 94% at a mean time of 5.6 months (3–19). Two patients with subtrochanteric femoral fractures failed to achieve union secondary to inadequate fracture stabilisation, persistent unfavourable biological environment and systemic co-morbidities. One patient developed synostosis attributed to the BMP-7 application. This study demonstrates BMP-7 implanted in a bovine-derived collagen paste is an effective adjunctive treatment for resistant non-unions in the upper and lower limb.

Introduction

Impaired bone healing and non-union affects between five and ten percent of all fractures.[1] Non-unions can be difficult to treat and may have devastating effects on patients, often requiring multiple operations, prolonged periods of recovery, causing significant psychosocial and functional disability.[2,3] Hypertrophic non-unions are associated with adequate vascularity and favourable biological environment. They require mechanical stabilisation for callus progression to occur at the fracture site. Atrophic non-unions are associated with inadequate vascularity and generally require a biological stimulus in addition to mechanical stability for healing to occur. Autologous bone grafting (ABG) has osteogenic, osteoinductive and osteoconductive properties and is the gold standard biological treatment for diaphyseal non-union.[4,5] However limited availability and complications related to its use such as further surgery, increased hospital stay, wound infections, discharging sinuses and chronic pain may limit its use.[6–10] When ABG has failed to stimulate healing in a non-union or where there is a contraindication to use, alternative biological enhancements have been sought to promote fracture healing.

In 1965 Marshall Urist[11] first hypothesised that certain proteins were capable of inducing new bone formation and subsequently named them bone morphogenic proteins (BMPs). BMPs are members of the transforming growth factor-beta superfamily and stimulate bone healing by promoting chemotaxis and the proliferation and differentiation of mesenchymal stem cells into chondrogenic and osteogenic cell lines. Fifteen BMPs have been discovered in humans.[12] In May 2001 the US Food and Drug Administration approved BMP-7 for the treatment of tibial non-unions. BMP-7 has subsequently been shown to stimulate union in tibial non-unions and posterolateral spinal fusion,[13–16] however few studies have evaluated their effects at other sites.[17] The aim of the present study was to investigate the safety and efficacy of local implantation of BMP-7 for the treatment of resistant non-unions in the upper and lower limb.

Methods and materials

Between 2003 and 2009, fifty-two consecutive patients with persistent non-unions were treated with application of composite paste consisting of BMP-7 and bovine bone-derived collagen with or without revision of fixation. Indications for implantation included persistent non-union despite previous surgery that

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Table 1
Demographics and clinical profile of the patients.

Case	Age	Sex	Site	Initial injury	Initial treatment	Number of operations pre-index operation	Type of non-union	ABG before index operation?	Additional operation	Lag-time	Follow-up	Time to union	Complications
1	61	M	Humerus	Closed	IM nail	4	A	Y	Revision ORIF	48	24	19	Stiff shoulder
2	30	M	Tibia	GA 3b	External fixator	2	A		TSF	5	19	9	Stiff Ankle
3	56	M	Tibia	GA 3a	Taylor Spatial frame	2	A	Y	ORIF	32	10	5	Repeat OP1 insertion
4	43	M	Femur	GA 3b	External fixator	2	A		ORIF	9	16	7	
5	22	M	Tibia	Infected non-union	Plating	2	A		Ilizarov	24	9	8	
6	48	F	Tibia	Closed	ORIF	2	A		ORIF	14	6	12	
7	48	M	Failed ankle fusion	Closed	External fixator	2	A	Y	IM nail	36	8	14	Screw backout
8	45	M	Tibia	Closed	IM nail	1	A			4	11	6	
9	24	M	Tibia	GA 3b	External fixator	1	A			24	5	5	
10	20	M	Tibia	Infected non-union	ORIF	2	H		Taylor spatial frame	18	7.5	6	
11	74	F	Tibia	Closed	IM nail & ABG	4	A	Y	ORIF	36	8	4	
12	77	F	Ulnar + Radius	Closed	ORIF	1	A			12	6.5	5	
13	66	M	Tibia	Closed	Ilizarov	2	A		ORIF	24	9	5	Ankle stiffness
14	55	M	Femur	Closed	IM nail	2	A		ORIF	12	6	4	
15	40	M	Tibia	Infected non-union	ORIF	2	A		TSF and bone transport	24	5	6	
16	54	M	Humerus	Closed	ORIF	2	A		ORIF	38	42	11	
17	60	F	Femur	Closed	ORIF & ABG	2	A		Revision IM nail	36	33	Failed to unite	
18	65	M	Femur	Closed	IM nail- Bilateral	3	A		Revision IM nail	18	34.5	7	
19	66	F	Tibia	GA 3b	IM nail	2	A		Ilizarov	36	34.5	12	
20	43	F	Tibia	Closed	IM nail	1	A			46	32.5	8	Superficial wound infection
21	34	F	Tibia	GA 3a	IM nail	2	A		ORIF	12	25.5	10	
22	43	M	Femur	Closed	Ilizarov	2	A		ORIF	36	19.5	7	
23	52	M	Femur	Closed	IM nail & ABG	5	A		ORIF	120	19.5	7	
24	81	F	Femur	Closed	IM nail	1	A			11	14.5	Failed to unite	
25	54	M	Tibia	Closed	External fixator	1	A	Y		9	15	4	Superficial wound infection
26	34	F	Femur	Closed	ORIF	2	A		ORIF	12	9	6	
27	47	F	Ulnar	GA 3b	ORIF + ABG	4	A	Y	ORIF	43	7	4	
28	50	F	Femur	Closed	IM nail	2	A	Y	ORIF	26	7.5	5	
29	40	M	Humerus	Closed	ORIF	4	A	Y	Ilizarov	16	4	4	Proximal pin backout
30	69	F	Humerus	Closed	IM nail	2	H		ORIF	13.5	6	4	
31	27	F	Clavicle	Closed	ORIF	2	A	Y	ORIF	6	4	3	
32	35	M	Ulnar	Closed	ORIF	2	A	Y	ORIF	7.5	12	6	
33	71	F	Radius	Closed	ORIF	2	A	Y	External fixator	6	7	3	
34	67	M	Humerus	Closed	Non-operative	2	A		ORIF	11	7.5	8	
35	45	M	Humerus	Closed	ORIF	1	A	Y		18	32.5	10	
36	81	F	Humerus	Closed	ORIF	2	A	Y	ORIF	20	16	4	
37	76	F	Humerus	Closed	IM nail	2	A		ORIF	14.5	11	6	
38	43	M	Clavicle	Closed	ORIF	2	A		ORIF	7	5.5	5	
39	59	M	Clavicle	Closed	ORIF	2	A		ORIF	10	14	4	
40	81	F	Humerus	GA 3a	External fixator	2	A		ORIF	5	10	6	
41	40	F	1st tarso-metatarsal joint	Closed	Fusion	2	A	Y	ORIF	36	6	Failed to unite	
42	50	F	5th Metatarsal	Closed	Corrective osteotomy & fixation	3	A	Y	ORIF	23	5	3	
43	61	M	Humerus	Closed	Non-operative	3	A	Y	ORIF	18	12	4	

44	74	F	Failed subtalar joint fusion	Closed	Non-operative	2	A		ORIF	15	5	4	
45	68	M	Tibia	Infected non-union	IM nail	2	A		Ilizarov	24	9	died	
46	38	M	Tibia	Closed	IM nail	2	A		Revision IM nail	12	8	4	
47	42	M	Tibia	GA 3b	ORIF	4	A		Ilizarov	14	11	7	
48	53	F	Tibia	GA 3a	IM nail	2	A	Y	Ilizarov	16	14	5	
49	74	M	Tibia	Closed	IM nail	2	A		Taylor spatial frame	15	12	4	
50	49	M	Tibia	Infected non-union	IM nail	3	A	Y	Taylor spatial frame	18	13	5	
51	52	M	Failed ankle fusion	Infected non-union	Internal fixation & ABG	2	A		Taylor spatial frame	12	9	10	
52	60	F	Tibia	Closed	IM nail	2	A		Revision IM nail	14	9.5	4	

GA = Gustilo-Anderson; ORIF = open reduction and internal fixation; IM Nail = intramedullary nail; ABG = autologous bone graft.

required biological enhancement at the fracture site. The indications for revision of fixation were fatigue failure, lack of fracture stability or persistent large gap at the fracture site. Contraindications to implantation included active infection, rheumatoid arthritis and any systemic inflammatory disease. Clinical data was collected retrospectively on patient demographics, site and type of initial injury (open or closed classified using the Gustillo-Andersen Classification [18]), initial treatment, number of subsequent operations prior to application of BMP-7, type of non-union, whether ABG had been used in previous operations, time from initial injury to BMP-7 application, follow-up, time to union and complications (see Table 1).

There were 30 males and 22 females with a mean age of 52.8 years (20–81). Thirty-six patients (70%) had closed injuries, 6 (11%) had infected non-unions, 6 (11%) had Gustillo-Andersen 3b open injuries and 4 (8%) had Gustillo-Andersen 3a injuries. Fifty (96%) were atrophic non-unions and two (4%) were hypertrophic. Forty-five patients (87%) had revision of internal fixation with insertion of BMP-7 to the non-union site. The remainder had application of BMP-7 composite paste only. Patients had undergone a mean of 2 (1–5) operations prior to implantation of BMP-7. Eighteen patients (35%) had previously undergone ABG to the fracture site. The mean time from initial injury to application of BMP-7 was 21.5 months (5–120).

In all patients recombinant human BMP-7 (Osigraft, Stryker) was applied directly to the fracture site after the bone ends were freshened and non-union tissue debrided. Each unit contained 3.5 mg of recombinant human BMP-7 mixed with 1 g of type I bovine bone collagen.

Before use, the BMP-7 is wetted with 3 ml of sterile 9 mg/ml sodium chloride solution for injection. The vial is gently swirled to aid in mixing and then allowed to stand for at least 2 min whilst the product expands to a maximum volume (4 ml). The reconstituted BMP-7 was removed from the vial with a spatula placed at the site of the non-union site. In some cases, to increase the volume and as a graft expander tri-calcium phosphate crystals were mixed with reconstituted BMP-7 to fill the bony defects.

When fatigue failure of the original metalwork, lack of fracture stability or a large gap at the fracture site was present the fixation was revised to a relative stability construct (Fig. 1). Intra-operative bone tissue specimens were sent for microbiological analysis in all cases. Intravenous Flucloxacillin and Gentamicin were administered after microbiological specimens were taken. Postoperatively two further doses of flucloxacillin were given. Thromoboprophylaxis consisted of thromboembolic deterrent stockings, early mobilisation and low-molecular weight heparin (40 mg subcutaneous enoxaparin) for 7–10 days.

Clinical and radiological follow-up was performed at six weeks, three months, six months, one year and annually thereafter until union was achieved (Fig. 2). Data on clinical and radiological union, patient satisfaction and visual analogue pain score was recorded. Radiological union was defined as the presence of bridging callus on at least three cortices visible on two plain radiographs. Clinical union was defined as no tenderness or movement at the fracture site with no pain on functional loading. Additionally a modified Anatomic, Economic and Functional scoring system (Modified AEF) was used to assess functional outcome.[19] The anatomic grade was assigned from the roentgenograms: A_0, pseudoarthrosis; A_1, unilateral pseudoarthrosis; A_2, insufficient unilateral bone mass; A_3, contiguous union without hypertrophy; A_4, solid union of the fracture site. The economic grade was assigned as follows: E_0, unable to work; E_1, no gainful employment; E_2, able to work but did not return to previous occupation; E_3, returned to previous occupation on a part-time or limited status; E_4, returned to previous occupation without restrictions. The functional grade was rated as follows:

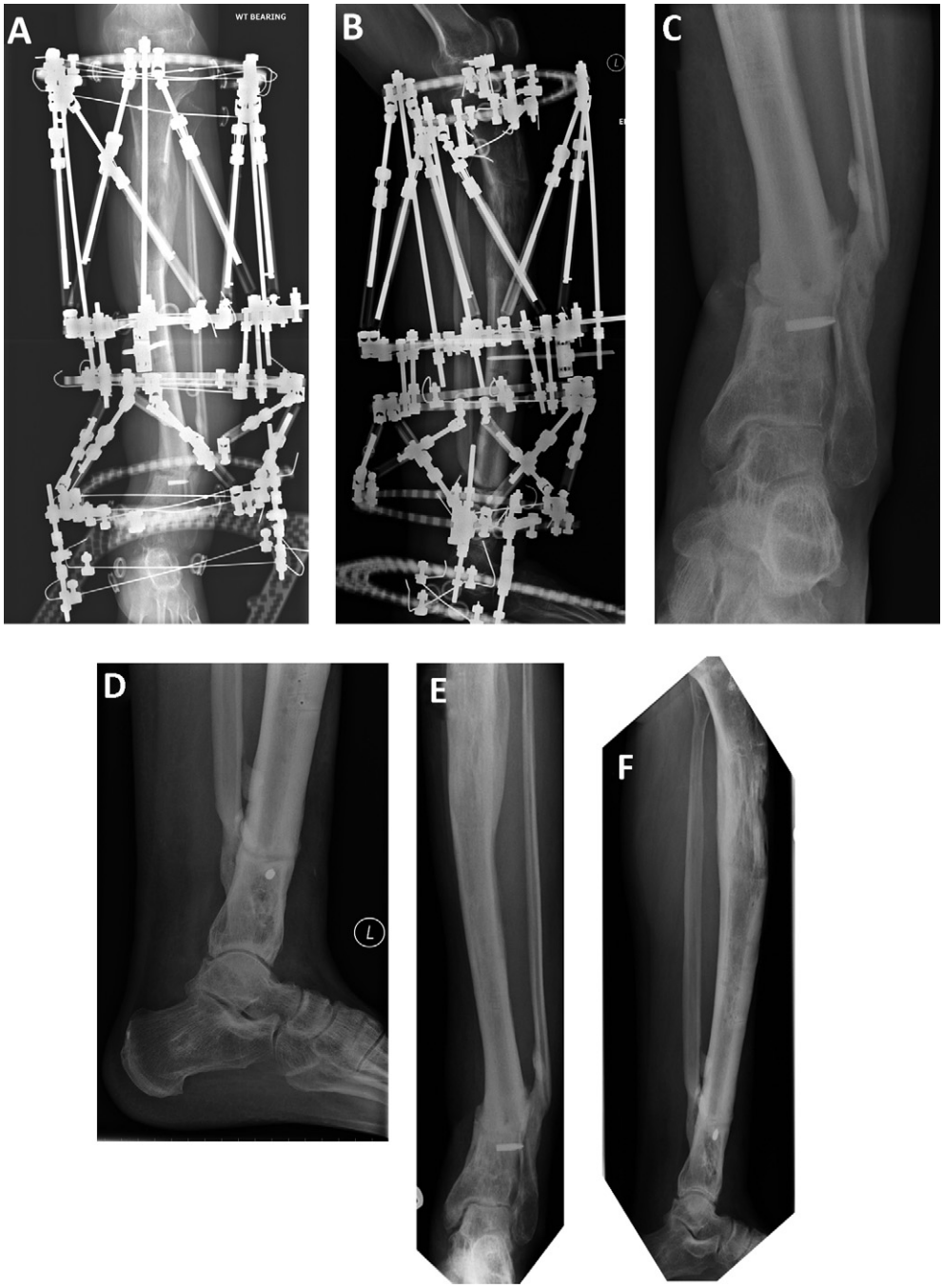

Fig. 1. Immediate postoperative anteroposterior (a) and lateral (b) radiographs of a non-united open distal tibial fracture following BMP-7 application to the docking site. Anteroposterior (c) and lateral (b) radiographs taken 3 months postoperatively demonstrate radiological signs of healing. Anteroposterior (e) and lateral (f) radiographs demonstrate the fracture had completely united by 5 months.

F_0, motion at the fracture site; F_1, level of pain is same as before the operation, able to perform all activities of daily living; F_2, occasional extremity pain, able to perform activities of daily living; F_3, no pain able to perform all activities except sports; F_4 complete recovery, no recurrent episodes of pain and unrestricted activity.

Results

One patient died during follow up from unrelated causes. Fifty-one patients were available for review with mean follow-up 13.2 months (4–42).

Union

Clinical and radiological union was achieved in 48 of 51 patients (94%). The mean time to union was 5.6 months (3–19). Patients with prolonged times to union showed early signs of radiological union at 8–9 months postoperatively with a mechanically stable construct at the fracture site, therefore a decision to allow more time to enable callus progression to occur was taken.

The three patients who failed to unite their fractures required revision surgery and are currently under review. Two of these patients had atrophic non-unions of subtrochanteric femoral fractures. Both of these non-unions were associated with segmental bone defects greater than 2 cm in length. All 10 open

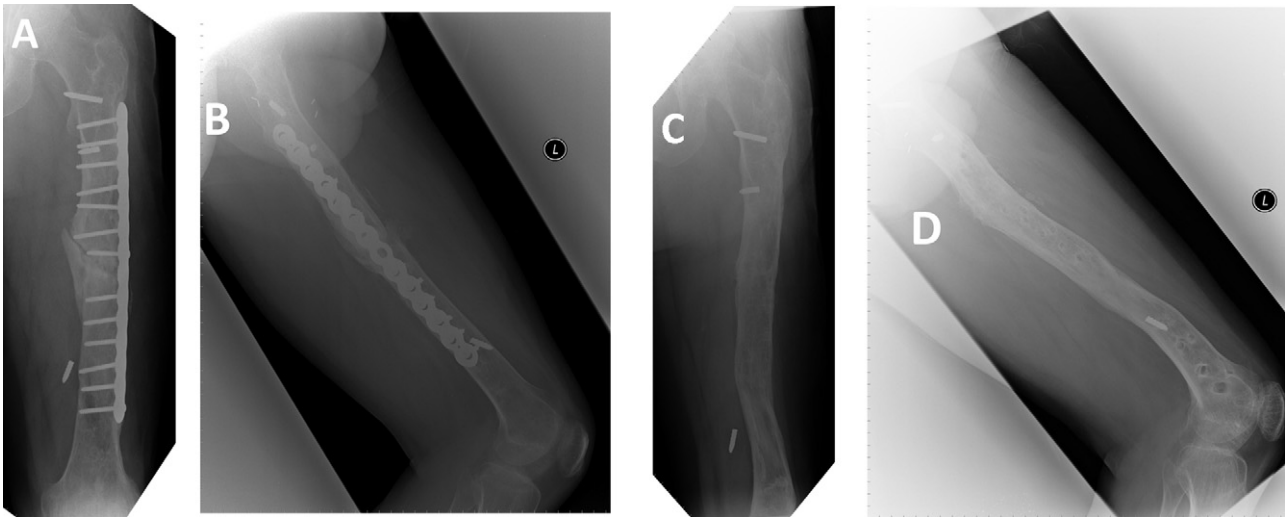

Fig. 2. Anteroposterior (a) and lateral (b) radiographs of the femur demonstrate an established proximal femoral non-union that had failed to unite following previous autologous cancellous bone grafting and revision of internal fixation. Six months following BMP-7 application to the fracture site anteroposterior (c) and lateral (b) radiographs show the fracture has united. The metalwork has been removed.

fractures united after application of BMP-7, however one patient failed to unite following initial application of BMP-7 and required a second application of BMP-7 with revision of internal fixation in order to successfully unite. This patient sustained a Gustillo-Andersen 3a tibial shaft fracture and was initially managed with a circular frame. The patient developed atrophic non-union and subsequently underwent open reduction and internal fixation with ABG. This failed to unite the fracture and BMP-7 was applied without revision of internal fixation. The fracture did not unite and further surgery was required which involved revision of internal fixation and further BMP-7 application. The fracture subsequently united at 5 months.

Functional outcome

Subjectively 42 patients (82%) were very satisfied with their outcome, 5 (10%) were somewhat satisfied and 4 (8%) were not sure. On the modified AEF scoring system 25 patients (49%) were A4 E4 F4 and considered as excellent outcomes. Nine patients (18%) were A4 E4 F3 and considered good. Three patients (6%) were A4 E3 F3 and considered fair. Fourteen patients (27%) were not included in the scoring system as they had retired from their occupation.

Complications

Eleven patients developed a complication (22%). Two patients developed superficial wound infections, which resolved after a course of oral antibiotics. Three patients failed to unite their fractures and are currently being managed for persisting non-unions. One patient required a repeat BMP-7 application with revision of internal fixation in order to unite. Three patients developed significant joint stiffness that affected function. One of these patients, who had originally sustained an open distal tibial fracture, developed distal tibio-fibular synostosis and post-traumatic ankle osteoarthritis (Fig. 1). One patient developed pin loosening in a circular frame and one patient developed loosening of an intramedullary nail locking screw. No systemic or allergic reactions were encountered after application of BMP-7.

Discussion

The treatment of impaired fracture healing is a challenging and increasingly common problem due to the greater incidence of high-energy injuries and longer life expectancies of patients. Hypertrophic non-unions have adequate vascularity but lack sufficient mechanical stability to allow callus progression to occur. Atrophic non-unions are more difficult to treat as they are associated with an inadequate 'biological environment' which may be the result of inadequate vascularity, soft tissue interposition, poor bone-on-bone contact or systemic factors such as smoking, malnutrition, age and co-morbidities. Their management requires biological enhancement in combination with mechanical stability.

Autologous cancellous bone grafting has osteogenic (osteoprogenitor cells), osteoconductive (lamellar bone and minerals) and osteoinductive (growth factors and BMPs) properties and provides the optimal biological stimulus for bone healing.[5,6] However ABG has limited availability and is not without risk. One study of 414 patients who underwent iliac crest ABG showed 10% had minor complications which included superficial wound infections, seromas and minor haematomas. Six percent had a major complication which included herniation of abdominal contents, neurovascular injury, deep infections and haematomas requiring surgical intervention.[20] When ABG has failed to unite a fracture or where there is a contraindication to its use, BMP-7 has been proposed as an osteoinductive agent that can stimulate fracture healing.[21,22]

Friedlaender et al.[13] were the first to establish BMP-7 as an osteoinductive agent capable of enhancing bone healing. They studied 124 aseptic tibial non-unions and compared the efficacy of BMP-7 ($n = 63$) to ABG ($n = 61$) and found union rates of 62% and 74% respectively at nine months. Infections were lower in the BMP-7 group and the researchers concluded that BMP-7 application was safe, and although not as effective as ABG at promoting union, avoided the complications associated with its use and should therefore be considered as an alternative.

Two BMP glycoproteins have been described for use in humans; BMP-2 and BMP-7. Both belong to the transforming growth factor-β superfamily and can be manufactured using recombinant DNA techniques.[23] BMPs have been shown to induce cartilage and bone formation by guiding and modulating differentiation of mesenchymal stem cells into osteogenic lineages.[24] BMP-7 has been shown to enhance fracture healing in the treatment of open tibial fractures, distal tibial fractures, tibial non-unions, scaphoid non-unions and atrophic long bone non-unions.[25–28]

Dimitriou et al.[25] performed a prospective study on 26 fracture non-unions treated with BMP-7 alone (31%) or in combination

with ABG (65%) or freeze dried allograft (4%). Patients had undergone a mean of 3.2 previous operations and 17 patients (65%) required additional fixation. Union was achieved in 92.3% of patients at a mean time of 5.6 months. One patient had recurrence of deep-seated infection and required below knee amputation. The infection complicated the non-union and was not attributed to the application of BMP-7. The researchers concluded that BMP-7 combined with ABG was a treatment option for persistent fracture non-unions. In the current study we did not use ABG as an adjunct and instead used a bovine-derived collagen paste for osteoconduction and achieved a similar union rate (94%) at a similar mean time to union of 5.6 months (3–19). Patients had undergone a similar number of prior operations and 87% of patients required further fixation. Host bone incorporates into ABG by creeping substitution and is associated with less inflammatory reaction than bovine bone-derived collagen paste which likely explains the longer mean time to union in the current study.

Few studies have reported on the use of BMP-7 in the upper limb.[26–28] Bong et al.[26] achieved union in 23 patients with atrophic humeral diaphyseal non-unions who were treated with compression plating or intramedullary nailing in combination with BMP-7 implantation. Van Houwelingen et al.[27] achieved union in six patients with humeral shaft non-unions who underwent plating in conjunction with allograft strut and local implantation of BMP-7. Bilic et al.[28] randomised 17 scaphoid non-unions to 3 groups and found that BMP-7 in combination with allogenic bone graft had similar outcomes to ABG and concluded that harvesting ABG may be avoided. We achieved union in three cases of atrophic clavicular non-union at a mean time of 4 months with no adverse events recorded.

Non-union occurred in three patients in the present study. Two of these patients had atrophic non-unions of subtrochanteric femoral fractures. Both of these non-unions were associated with segmental bone defects greater than 2 cm in length. The persistent non-union was attributed to inadequate fracture reduction with minimal host bone-on-bone contact, inadequate fracture stabilisation and systemic co-morbidity. In such cases a structural graft or acute shortening would have been more suitable and we would not recommend BMP-7 with bovine bone-derived collagen paste when significant bone defects (>2 cm in length) are present.

Although we identified no adverse reactions with the use of BMP-7 in the current study, one patient developed a distal tibiofibular synostosis which is likely related to the use of the BMP-7. Concerns have been raised about the safety of BMP-2, which was initially considered a safe treatment. Carragee et al.[29] performed a systematic review comparing the adverse effects and outcomes between industry sponsored studies and Food & Drug Administration (FDA) documentation in the use of spinal fusions. No adverse events were reported in any of the 13 industry sponsored trials, however the FDA documentation data reported an estimated 40% greater risk of adverse events associated with the use of BMP-2 which included subsidence, infection, ectopic bone formation, osteolysis and poorer global outcomes.

There are limitations to this study. There was no randomisation or control group for comparison with other techniques. Selection bias with a heterogenous study population who had already had a variety of treatments for established non-union may have confounded the results. Interviewer bias and adjustment of internal fixation will also have confounded the results.

This study demonstrates OP-1 (BMP-7) implanted with bovine-derived collagen paste may be used to treat resistant diaphyseal non-unions in the upper and lower limbs which have not responded to previous revision surgery or ABG. It results in similar union rates to the use of BMP-7 in combination with ABG, however time to union is increased and we would caution against its use when significant bone defects exist.

Conflicts of interest

None.

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