Research Article

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Treatment of Resistant and High-Risk Humeral Non-union Cases with rhBMP7

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Abstract

Introduction: Non-union of the humeral shaft is a rare condition. In these patients, more stable fixation with or without autograft results in nearly 95% union rate. The purpose of this study was to evaluate bone union following use of recombinant human bone morphogenetic protein-7 (rhBMP7) for treating humeral non-union.

Material and methods: This was a prospective study of resistant non-union cases treated by repeated fixation and addition of rhBMP7. The case series consisted of 16 patients with an average age of 53.8 years (24-71). Patients presented with non-union of the humeral shaft and had experienced at least one failed attempt at surgical repair. Osigraft® (rhBMP7) was added to the non-union site after decortication, medullary canal reaming and fixation with one or two plates. The average time elapsed between the initial fracture and the second revision was 31 months (5-103). The patients had undergone an average of 2.3 procedures (1-6).

Results: All patients were reviewed after at least 24 months of follow-up. No neurological complications were reported. One failure occurred in a non-compliant patient with septic non-union who had undergone four previous procedures. The other patients experienced bone union after an average of 12.4 months (6-14), with no further procedures required. The patients were able to return to their normal daily activities.

Conclusion: Failure of the initial fracture treatment (unstable fixation, postoperative bone defect) is the primary cause of non-union. Although autograft is the gold standard treatment for non-union cases, the course of action to take if this primary strategy fails has not been defined. During secondary use (due to failed autograft procedure) and when there is no requirement for a structural graft (humerus can be shortened), providing stable fixation and adding a growth factor leads to bone union even in a septic environment.

Keywords: Humeral non-union, BMP, Resistant non-union, Osteosynthesis, Plate

Abbreviations: CHO: Chinese Hamster Ovary; DBM: Demineralized Bone Matrix; IM: Intramedullary; OP-1: Osteogenic Protein-1; rhBMP7: Recombinant Human Bone Morphogenetic Protein-7

Introduction

Although rare, non-union of the humerus is normally the result of inadequate fixation, such as use of a device that does not control rotation (typically a paediatric nail being used in adults), and the presence of specific aggravating

complications (radial palsy) [1]. The humerus has two anatomical features that must be taken into account when planning treatment: the rotation must be fully controlled and the bone can be shortened. Fixation with two plates may be necessary to control rotation [2]. Adding a graft to fill a defect may not be relevant as the bone is not

weight bearing. In cases of non-union, a corticocancellous autograft in combination with plate fixation appears to be the best treatment strategy [3]. Although treatment of humeral non-union is well defined, few studies have looked into failed non-union repair, resistant non-union cases and non-union cases where the biological environment is compromised [4],[5],[6]. The purpose of this study was to evaluate bone union following compassionate use of bone morphogenetic protein-7 (BMP7), an osteogenic growth factor, for treating humeral non-union.

Material and Methods

Patients

This was a single-centre, prospective, observational study without a control group during 4 consecutive years. Two types of patients had been treated with BMP7. One group consisted of patients with resistant non-union, meaning the non-union had not healed despite at least one specific treatment being carried out for this non-union (at least two procedures performed prior to BMP7 application). The other group consisted of patients at high-risk of non-union, meaning fractures with a high risk of not healing because of local factors (open fracture) or systemic factors (smoker, diabetic, non-union in another location); these fractures had progressed to non-union but had specifically been treated for non-union (only one procedure-fracture fixation-performed before BMP7 application). In all cases the non union and the bone defect were located at the medium third of the humerus shaft.

Patients were included if they had a resistant or high-risk diaphyseal or metaphyseal humeral non-union that had been present for at least 6 months. The case series consisted of 16 patients with an average age of 49 years (24-71) who had a resistant or high-risk non-union (Table 1). They were treated and then followed prospectively. The final evaluation was performed by a surgeon who was not involved in the procedures or patient care. The initial fracture was located in the mid-shaft in 11 cases, upper shaft in one case, and distal shaft in three cases and was supracondylar in one case. Four patients had accompanying radial palsy, one had brachial plexus involvement and three had open fractures. One patient had non-fusion of an elbow arthrodesis that had been performed because of post-traumatic osteoarthritis. Initially, three fractures had been operated with retrograde pinning, two with a non-locked intramedullary (IM) nail, and two with locked IM nail, one with a cast, seven with a single plate and one with an external fixator. Seven of these initial constructs were deemed unstable. Two patients presented with

non-union of another bone at the time of the humerus fracture. Two patients were diabetic, two were confirmed smokers with more than 20 pack-years, and one smoked about 10 pack-years. These 16 fractures had not healed after 9 months. Nine were re-operated at least once using a standard technique (new fixation device, decortication, corticocancellous bone graft or intramedullary reaming) before the BMP7 procedure. The BMP7 procedure was the first surgical procedure for the other seven patients.

At the time the BMP7 was added, the fracture symptoms had been present for 24.4 months (5-103) and an average of 1.9 procedures (1-6) had been performed. Four patients had already received a bone graft and one had received biphasic calcium phosphate cement. There were 12 cases of atrophic non-union, 1 of eutrophic non-union, 2 of hypertrophic non-union and 1 of non-union with a 3 cm bone defect. Two of the non-union cases were considered septic without fistula (*Staphylococcus epidermidis*, *Staphylococcus aureus*) and one was considered septic with fistula (no samples collected). In every patient, the existing fixation device was removed and replaced with standard or locking plates, and then BMP7 was added. Upon re-operation with the addition of BMP7, 4 of the 16 patients also received an iliac crest autograft because the surgeon determined the resulting limb shortening was unsightly. Fracture union was determined by an independent observer using A/P and lateral radiographs, with CT scans being consulted if radiographic findings were ambiguous. Union was defined as the presence of two cortices in the two perpendicular planes, thus four intact cortices.

Technique

BMP7 (also known as Osteogenic Protein-1, OP-1) is a protein that promotes bone formation by inducing differentiation of mesenchymal stems recruited to the implantation site from the bone marrow, periosteum and muscle. Once bound to cell surface receptors, it triggers a cascade of cellular events leading to the formation of chondroblasts and osteoblasts. The commercially available form of BMP7 (Osigraft®, Stryker/Olympus) contains 3.5 mg of recombinant human OP-1 (eptoterminalfa) as the active ingredient and bovine collagen as a resorbable carrier. Each vial contains 1 g of powder. Each vial of Osigraft® is reconstituted with 2 to 3 ml of sterile 9 mg/ml sodium chloride solution (0.9% w/v) prior to use. Eptoterminalfa protein is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. Bovine collagen is derived from diaphyseal bone and consists mainly of type I collagen. The European marketing authorization for Osigraft® is for treatment of tibial non-union of at least 9

months duration, secondary to trauma, in skeletally mature patients, in cases where previous treatment with autograft has failed or autograft use is not feasible. Osigraft® is contraindicated in children and adolescents (less than 18 years old) and skeletally immature patients [7].

Osigraft® implantation

In this case series, any septic or necrotic tissues were resected, the medullary canal was reamed and the surrounding bone was decorticated. The existing fixation was evaluated and modified as needed, and in some cases completely revised (addition of second plate or removal of nail and replacement with plate). A bone graft was added if warranted by the local conditions observed during the procedure, even if no bone defect was present. The Osigraft® was implanted by mixing it with blood or bone marrow at the end of the procedure, before wound closure. When reconstituted, Osigraft® has the consistency of wet sand; this facilitates its implantation and placement at the bone-graft site. If no graft was added to the non-union gap, Osigraft® was placed in the medullary canal. A haemostatic compress was placed around the non-union site for drainage.

Results

All patients were reviewed after at least 24 months of follow-up (Table 2). No neurological complications occurred, but one patient was under treatment at a regional pain centre for chronic pain. Union was achieved in 15 of the 16 cases (93.7% union rate); there was one failure. The average time to union was 12.75 months. In the 16 cases where rhBMP7 was combined with a change in the fixation device, union was obtained in 15 of them. In 5 of these 15 cases, changing the fixation method increased the stability of the fracture site. Union was achieved in three of the four cases where autograft was also used. The infection resolved in the three cases of septic non-union and union occurred in two of these cases after rhBMP7 addition.

The only failure was in a 59 years-old male with a eutrophic, septic non-union complicated by radial palsy following a Cauchoux type 2 open fractures of the upper third of the humerus, which had already undergone four prior procedures, including bone grafting. A bone defect was present after his infection site underwent debridement; this defect was then treated with the induced membrane technique. BMP7 was added during the second phase of this technique, in combination with an iliac crest autograft. On day 10, this patient's wound showed signs of pruritus

and erythema but no signs of infection. The episode resolved spontaneously 7 days later without systemic or local treatment. This skin condition was highly suggestive of an allergic reaction, likely related to rhBMP7. However, there is no proof of an allergic reaction to rhBMP7 because no samples were collected for laboratory analysis. In the month after the procedure, the patient spent 3 weeks building a shed and the two plates broke after 8 months.

In the 15 patients where the fracture had healed, shoulder abduction and forward flexion were 97% and 92% of the other side. The elbow's flexion-extension range was 126°, which was 89% of the contralateral side in the 14 patients with a mobile elbow. The worst functional outcomes were in a patient with type I regional pain syndrome (Figures 1 to 3).

Figure 1: 70-year-old man with non-union of the right humerus after 2 operations with autograft and allograft in addition to fracture treatment. Radial paralysis occurred during the first intervention and a painful complex regional syndrome of type 1 with stiffness of all the articular chains of the upper limb, complicated the evolution.

At 14 months of the fracture, paralysis is resolute, there is no fistula, and the integuments are non-inflammatory despite positive leukocyte scintigraphy.

Figure 2: Radiographic evolution of consolidation at 1 month (a), 6 months (b), 12 months (c) and 22 months (d).

Figure 3: Useful mobility of the shoulder and elbow.

Discussion

Limitations

Although our series of patients was followed prospectively, only a small number of patients were included and there was no control group. However,

this is the case for most studies on humeral non-union. Another limitation was the inclusion of cases treated on a compassionate use basis, making the patient population heterogeneous. Our definition of radiological union (4 cortices) was different than the one typically used in published studies in this area (3 cortices).

Treatments used for humeral non-union

The incidence of non-union in the humeral shaft varies between 15% and 30%. This is slightly higher than in other long bones; these fractures are rare and inadequate fixation methods are still frequently being used [8]. Half of the patients in our study had undergone initial fracture fixation with retrograde pinning or a non-locked nail. Treatment of humeral non-union must take into consideration both the mechanical and biological environment, as with other long bones. However, the humerus is different because it is not a weight bearing bone; it undergoes rotational loading and may be shortened by several centimetres if a bone defect is present. To improve stability, the existing fixation method may need to be revised or completely replaced by an altogether different device.

Three types of fixation methods have been described in published studies: plates (standard or locking), intramedullary nails (with or without reaming) and external fixator [3]. The union rate was between 90 and 100% in studies where plate fixation was used. A series of 30 cases of diaphyseal humeral non-union, mainly in the middle-third and initially fixed by pinning, was reported by Segonds, Alnot and Masméjean [1]. All cases were re-operated and treated by plating and cancellous bone autograft. Union was achieved in all cases in 4 months. Half the cases experienced improved shoulder and elbow function. There were two cases of transient radial nerve contusions. If intraoperative stability is insufficient, a second plate can be added [3],[9]. If the fracture was initially pinned, it may not be sufficient to simply ream the medullary canal and change out the fixation device. In some studies with fewer than 30 patients [10],[11],[12], the union rate was below 50% when the revision of the non-union was fixed with percutaneous nailing, without grafting. Although reaming seems to play a biological role, it cannot compensate for insufficient rotational stability. In other IM nailing studies, addition of an autograft improved the union rate, despite the need for an open procedure. External fixators are used because of theoretical advantages related to bone union, but their application in the upper limb has several disadvantages.

The union rate varies as a function of the fixation

Table 1: Characteristics of patients included in this series.

Case No.	Gender, age, risk factors	Initial injury		Type of non-union	Before BMP procedure		
		Type	Treatment		No. surgeries	Duration	Bone graft
H1	M 65 Tibial non-union and sepsis	Closed, middle third	Non-locked IM nail	Hypertrophic, septic	6	27 months	Yes, autograft
H2	M 59 Sepsis, radial palsy	Open, Type C2 Middle third, radial palsy	Retrograde IM nail	3 cm septic defect, radial palsy	4	103 months	Yes, autograft
H3	F 23	Closed Middle & distal thirds	LCP plate	Atrophic, aseptic, distal quarter	1	13 months	No
H4	M 59 Radial and ulnar palsy	Closed, spiral, upper third, radial and ulnar palsy	Metaizeau type pinning	Atrophic, aseptic, upper third, radial and ulnar palsy	2	16 months	No
H5	M 42 Radial nerve palsy	Closed, transverse, middle and distal thirds	Plate and bone substitute, radial palsy	Atrophic, aseptic, middle and upper thirds	1	13 months	Yes + Bone substitute
H6	M 58 Medial malleolus non-union Smoker	Elbow fusion for post-traumatic OA	Plate	Atrophic, aseptic non-union	2	54 months	No
H7	M 44 Non-union in forearm	Closed, distal humerus	Y-plate	Atrophic, aseptic	1	5 months	No
H8	M 70 Diabetes, radial palsy	Closed Middle & distal thirds	Conservative treatment, then plate with autograft and allograft	Eutrophic, aseptic with radial palsy	2	20 months	Yes Autograft and allograft
H9	F 63	Closed Middle & distal thirds	Non-locked IM nail	Atrophic, aseptic	2	54 months	No
H10	F 44 Very low vitamin D levels	Closed Distal third of shaft	Locked IM nail	Eutrophic, aseptic	1	5 months	No
H11	M 28 Drug addiction Superficial infection secondary to scratching	Closed Distal third of shaft	Plate	Atrophic, aseptic	1	12 months	No
H12	M 60	Closed Middle and distal thirds of shaft	Locked IM nail	Atrophic, aseptic	1	18 months	No
H13	F 69 Diabetes	Closed Proximal third of shaft	Metaizeau type pinning	Hypertrophic, aseptic	2	16 months	No
H14	M 33 Smoker, infection	Closed Distal third of shaft	Plate	Atrophic, septic	2	7 months	No
H15	M 38 Radial and ulnar nerve contusions Gunshot wound	Open, Type C2 Middle & distal thirds	Plate	Atrophic, aseptic	1	16 months	Yes Autograft
H16	M 29 Axillary artery & brachial plexus damage	Open, Type C2 Proximal third of shaft	External fixator	Atrophic, aseptic	2	12 months	No

F: female, IM: intramedullary, LCP: locking compression plate, M: male, OA: osteoarthritis

Table 2: Results of rhBMP7 application.

Case No.	Gender age risk factors	BMP combined with		Union		Time to union with BMP	Complications and side effects
		Fixation device change Better stability	Bone graft	BMP related?	No. of surgeries after BMP application		
H1	M 65 Tibial non-union and sepsis	Yes, plate	No	Yes	0	9 months	Successful
		Yes					No complications, no side effects
H2	M 59 Sepsis, radial palsy	Yes, plate	Yes, autograft 2nd stage, induced membrane technique	No	1	37 months	Failure
		No					Allergic-type skin reaction
H3	F 23	Yes, 2 plates	No	Yes	0	8 months	Successful
		No					No complications, no side effects
H4	M 59 Radial and ulnar palsy	Yes, plate	No	Yes	0	6 months	Successful
		Yes					No complications, no side effects
H5	M 42 Radial nerve palsy	Yes, LCP plate	Yes, autograft	Yes	0	11 months	Successful
		Yes					No complications, no side effects
H6	M 58 Non-union medial malleolus Smoker	Yes, plate	No	Yes	0	12 months	Successful
		No					No complications, no side effects
H7	M 44 Non-union forearm	Yes, 2 LCP plates	Yes, autograft	Yes	0	6 months	Successful
		No					No complications, no side effects
H8	M 70 Diabetes, radial palsy	Yes, 2 plates	No	Yes	0	14 months	Successful
		Yes					No complications, no side effects
H9	F 63	Yes, 2 LCP plates	No	Yes	0	14 months	Successful
		Yes					No complications, no side effects
H10	F 44 Very low vitamin D levels	Yes, 2 LCP plates	No	Yes	0	18 months	Successful
		Yes					No complications, no side effects
H11	M 28 Drug addiction Superficial infection secondary to scratching	Yes	No	No	1	12 months	Successful, but not BMP-related
		Yes					Superficial infection secondary to scratching (pruritus)
H12	M 60	Yes, 2 ULS plates with non-locked nail left in place	No	Yes	0	12 months	Successful
		Yes					No complications, no side effects
H13	F 69 Diabetes	Yes, 1 plate	No	Yes	0	12 months	Successful
		Yes					No complications, no side effects
H14	M 33 Smoking Infection	Yes, 2 LCP plates	No	Yes	0	9 months	Successful
		Yes					No complications, no side effects
H15	M 38 Radial and ulnar nerve contusions Gunshot wound	Yes, LCP plate	Yes, autograft 2nd stage, induced membrane technique	Yes	0	12 months	Successful
		Yes					Chronic pain, treated at CETD
H16	M 29 Axillary artery & brachial plexus damage	Yes, 2 plates	No	Yes	0	12 months	Successful
		Yes					Post-operative infection that did not interfere with bone union

F: female, LCP: locking compression plate, M: male

Type of study	Number of BMP cases	Avg. number of procedures and avg. time before BMP application	% of patients who had already received graft	Indication	Union rate	Avg. time to union	Complications and side effects
Johnson EE Prospective, observational	N=6 rhBMP + allograft	N/R 21 months (5–43)	N/R	Long bone non-union (6 in humerus)	100%	4 months (3–5)	No side effects No complications
Bong MR Prospective observational	N=23 rhBMP-7 + bone graft or substitute	1.3 procedures (0–3) N/R	N/R	Atrophic non-union of humeral shaft	100%	4.8 months (2.3–11.9)	4 early complications (1 severe, 3 non-severe) 4 late complications, including 1 ectopic ossification
Dimitriou R Prospective observational	N=3 rhBMP-7 2/3 + autograft	1 procedure 19.5 months (7.5–29.5)	33%	Long bone non-union (3 in humerus)	100%	N/R	No side effects No complications
Ronga M Retrospective observational	N=20 rhBMP-7	N/R N/R	N/R	Long bone non-union (20 in humerus)	85%	N/R	No side effects N/R

method. Kontakis et al. [3] compared all published humeral non-union studies. Plate fixation resulted in a 95% union rate (353/371 published cases), nailing resulted in a 72% union rate (135/187 published cases), and circular external fixation results in a 91% union rate (103/112 published cases). However, the addition of a bone graft was a confounding factor in the study: it was used in 95% of cases in the plate fixation cases, 79% of the nail fixation cases and 41% of external fixation cases. The Kontakis study also highlighted the complications related to the various types of fixation methods. There were more nerve-related complications when an external fixator was used (9%) relative to a plate (5%) or IM nail (3%) and there were more infections with the external fixator (60% pin infections, including benign and more severe cases) relative to plate (2%) or IM nail (4%) fixation. Complications associated with autograft harvesting were reported only in the studies where plate fixation had been used; the complication rate was 5.6% for the 352 cases evaluated.

Resistant and high-risk humeral non-union

Although several publications describe the use of different fixation methods for humeral non-union, very few have addressed cases of resistant non-union. In the resistant non-union cases, the search for more stable fixation is slowly gaining traction for optimisation of graft vascularisation.

Ring et al. [13] described a series of older patients (average age of 62 years) where two-thirds of patients had already undergone one surgical procedure. Use of a standard or locking, long (11-hole) or shaped plate with 6.5 mm cancellous bone screws in combination with autograft resulted in bone union in 91% of cases. In a series of resistant and sometime extreme cases of non-union (multiple recurrences), Kaminski et al. [14] reported that use of vascularised cortical-periosteal grafts harvested from the supracondylar section of the femur resulted in union after 6 to 11 months.

Although addition of an autograft in humeral non-union cases is not justified from a structural standpoint, it has been carried out by several surgical teams [3]. The main advantage of using autograft is that it provides three biological players (matrix, cells, and growth factors) in undefined, yet balanced amounts. Autograft contains 40% bone fragments larger than 100 microns; these fragments may contain bone progenitor cells [15]. This type of graft must not be washed. For non-union cases, some studies have shown that fewer progenitor cells are present in the bone marrow [16] and lower levels of certain circulating growth factors such as TGF-beta1 [17].

Unfortunately, few authors report the complication rate or donor-site complications in studies where autograft was harvested. In the Kontakis study [3], complications

associated with autograft harvesting were reported only in studies where plate fixation had been used; the complication rate was 5.6% in the 352 cases evaluated. The donor site complication rate was 44% in the Hierholzer study [2].

In cases of resistant non-union after failed repair attempt with autograft, and because of donor site complications, some teams have used growth factors. Hierholzer et al. [2] reported a retrospective study where an iliac cancellous bone autograft (45 patients) was compared to demineralized bone matrix (DBM) for the treatment of humeral non-union. The time between the fracture event and surgery was 14 months in the autograft group and 22 months in the DBM group. In both groups, it was the first failure and fixation was carried out with a plate. The union rate was similar in both groups, but iatrogenic complications related to autograft harvesting led the authors to recommend using DBM. Several studies with BMP7 have been published, but these do not include a control group (Table 3). Four humeral non-union studies have been published and they reported high union rates [18],[19],[20],[21]. However, the cases were not well described and no control group was included.

When our study is compared to published studies, our study is the first to describe growth factor treatment of resistant non-unions of the humerus. Hierholzer et al. [2] used growth factors (within the DBM), but not in cases of resistant non-union. This makes it difficult to compare our results with published results. The sample size ($n = 16$) in the current study is similar to other published studies that included a relatively small number of cases. When comparing our study to studies where a different biological substance (autograft, vascularised graft, DBM) was added, there is little difference in the union rates. The evaluation of functional outcomes (range of motion) in this study sets it apart from other published studies.

Use of BMPs in long bone non-union

Published studies on use of BMP in non-union cases are limited and difficult to compare to each other. Two types of studies have been performed: case series of resistant non-union with and without bone defects, and randomised controlled trials.

Case series

These are single cases or case series of non-union, mainly in the tibia and femur, which have not resolved despite one or two surgical procedures. These cases either

had large bone defects or were considered tight (stable) non-union with small defects (1 cm) [22],[23],[24],[25],[26]. Unfortunately, it is often difficult to determine if a bone defect existed in a particular case. Moreover, in some of the cases, BMP was used as a last resort before amputation. No control groups were included.

Two technical points make it challenging to analyse these studies. 1) The BMP is not added alone, thus it is difficult to attribute the procedure's success to the BMP. A carrier such as autograft or allograft is typically added. 2) In the absence of a true bone defect, it is quite difficult to follow the progression of bone healing on radiographs. Analysis of CT scans would have been helpful in this scenario.

Although the reported cases are dissimilar, two elements were emphasized by the authors: stable fixation and good soft tissue coverage. The BMP was always combined with a synthetic or bone carrier, then the BMP and carrier were placed within the resected non-union site. In a report of compassionate use in patients who had previously undergone multiple surgical procedures, addition of BMP resulted in rapid bone union (6 months) [27]. All of the published studies on long bone non-unions were performed with BMP7. Addition of BMP with a massive cancellous bone autograft is now being evaluated (induced membrane technique).

Randomised, comparative trials

Two such studies have been published: one study relates to open leg fractures with addition of BMP2 [28] and the other relates to tibial non-union cases treated with BMP7 [29]. In the subgroup of fractures where BMP2 was used, the results were the same as when the fracture site was reamed. In the non-union study where autograft was compared to BMP7, the patients in the BMP group had unfavourable characteristics (larger bone defects, higher number of smokers) but the results were not inferior to autograft. Although neither study showed BMP to be superior, the BMPs outcomes were similar to outcomes with autograft application, and there were significantly fewer cases of postoperative sepsis in the BMP groups. Specific adverse effects were rare and related mainly to local ossification [29]. Although there is a large body of basic research on the link between BMPs and cancer, which is a logical relationship given the ubiquitous nature of these growth factors, no cases of BMP-related cancer have been reported [30],[31].

Conclusion

At one point, orthopaedic surgeons and hurried readers believed that the problem of diaphyseal non-union was solved when bone growth inducers appeared on the market. They extrapolated the results of animal studies and applied them to their future patients. But in most cases, these animals had healthy bone, and had not undergone multiple surgical procedures and did not smoke. Moreover, the readers did not look at the time to union, which was always on the order of months. Even when the defect was made in a healthy bone, union required more than 1 year.

Now, and given our experience with resistant humeral non-unions (at least one failed autograft treatment) and high-risk non-unions (open fracture, palsy complication, systemic risk factors), use of BMP7 while following the standard non-union management principles shows that further procedures are unnecessary. The positive effect on bone union is even more consistent when the non-union is in the cortex, fixation is stable, the BMP is added to the medullary canal, and the patient is compliant. Since either bone marrow cells or bone inductive proteins can be used, it is important to carefully analyse past failures and successes, while attempting to assign each player their role in the bone union game. It is also important to respect well known, but sometimes forgotten, principles for managing long bone non-union. Rigour is more important than ever when designing and evaluating future studies. Currently the RhBMP7 is no longer available.

Declarations

No ethics approval was needed. All patients were consent to participate for data collection.

Consent for publication has been obtained from patients

All data generated or analysed during this study are included in this published article.

Competing interests

L.O. is Consultancies for FX Solution, Zimmer, Medartis, Evolutis, Wright.

S.E.R., F.L. and D.L. declare that they have no conflict of interest.

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S.E.R., F.L., L.O. and D.L. contributed to the design and

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