RhBMP-7 accelerates the healing in distal tibial fractures treated by external fixation

J. Ristiniemi,
T. Flinkkilä,
P. Hyvönen,
M. Lakovaara,
H. Pakarinen,
P. Jalovaara

From the University Hospital of Oulu, Oulu, Finland

External fixation of distal tibial fractures is often associated with delayed union. We have investigated whether union can be enhanced by using recombinant bone morphogenetic protein-7 (rhBMP-7).

Osteoinduction with rhBMP-7 and bovine collagen was used in 20 patients with distal tibial fractures which had been treated by external fixation (BMP group). Healing of the fracture was compared with that of 20 matched patients in whom treatment was similar except that rhBMP-7 was not used.

Significantly more fractures had healed by 16 (p = 0.039) and 20 weeks (p = 0.022) in the BMP group compared with the matched group. The mean time to union (p = 0.002), the duration of absence from work (p = 0.018) and the time for which external fixation was required (p = 0.037) were significantly shorter in the BMP group than in the matched group. Secondary intervention due to delayed healing was required in two patients in the BMP group and seven in the matched group.

RhBMP-7 can enhance the union of distal tibial fractures treated by external fixation.

Distal tibial fractures are difficult to treat. External fixation has been shown to give acceptable functional results with fewer severe complications when compared with internal fixation by a plate and screws.[1,2] In previous series, delayed union of the metadiaphyseal fracture has been a common finding, despite high levels of primary or early cancellous autografting.[1,3,4]

Bone morphogenetic proteins (BMPs) are members of the transforming growth factor-β (TGF-β) group of polypeptides containing growth and differentiation factors, which induce formation of bone by promoting the differentiation of mesenchymal cells into chondrocytes and osteoblasts. At least 16 different BMPs are known, of which BMP-2 and BMP-7 are currently commercially available.[5-8]

Recombinant (Rh)BMP-7, also known as osteogenic protein-1 (OP-1), is strongly osteoinductive.[5] The therapeutic potential of rhBMP-7 has been documented in many animal experiments and clinical trials. It can effectively heal articular cartilage in dogs,[9] defects of the long bones in monkeys,[10] skull defects in rats,[11] accelerate the healing of tibial fractures in goats[12,13] and induce spinal fusion in rabbits.[14] Its clinical efficacy has been shown in spinal fusion,[15,16] tibial nonunion[17] and fibular defects.[18] It also appears to be able to compensate for the detrimental effects of nicotine on spinal fusion.[19] A preliminary report has shown enhanced healing of open tibial fractures in man.[20]

We have examined the effect of rhBMP-7 on distal tibial fractures treated by external fixation. These are known to heal slowly and are often subject to numerous complications.

Patients and Methods

Between 1998 and 2004, 2904 tibial or malleolar fractures were treated in our hospital. Of these, 156 were tibial fractures within 5 cm of the ankle, in zone 43 of the Orthopaedic Trauma Association (OTA)[21] classification.

Treatment was provided by a two-ring hybrid external fixator for 67 of these fractures (Figs 1 and 2). This is our primary method of treating OTA type-A and type C fractures in zone 43 of the tibia since they are too distal for satisfactory management by intramedullary nailing. Within this group 20 fractures also received osteoinductive treatment with rhBMP-7 and bovine collagen (BMP group). The number of patients treated was approved by the hospital, and the local ethics committee agreed to the study. A group of 20 patients was created from the remaining 47, who were matched for age to within 15 years, gender, type of fracture, the shape of the proximal fracture, the defect

■ J. Ristiniemi, MD, Orthopaedic and Trauma Surgeon
■ T. Flinkkilä, MD, PhD, Orthopaedic and Trauma Surgeon
■ P. Hyvönen, MD, PhD, Orthopaedic and Trauma Surgeon
■ M. Lakovaara, MD, Orthopaedic and Trauma Surgeon
■ H. Pakarinen, MD, Orthopaedic and Trauma Surgeon
■ P. Jalovaara, MD, PhD, Professor of Orthopaedic and Trauma Surgery
Department of Orthopaedic and Trauma Surgery
University Hospital of Oulu, P.O. Box 90029, OYS, Oulu, Finland.

Correspondence should be sent to Dr J. Ristiniemi; e-mail: Jukka.Ristiniemi@oulu.fi

doi:10.1302/0301-620X.89B2.18230 $2.00

J Bone Joint Surg [Br] 2007;89-B:265-72.
Received 6 June 2006; Accepted after revision 19 September 2006

Fig. 1a

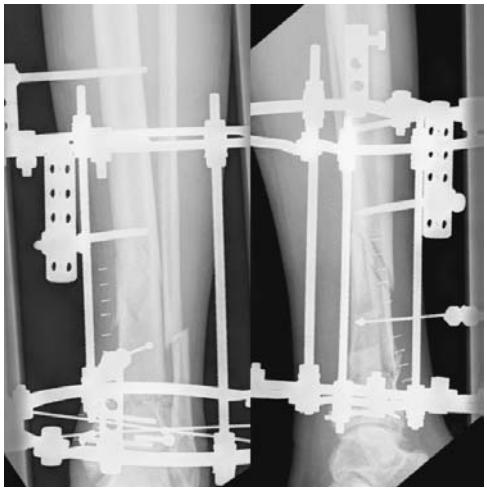

Fig. 1b

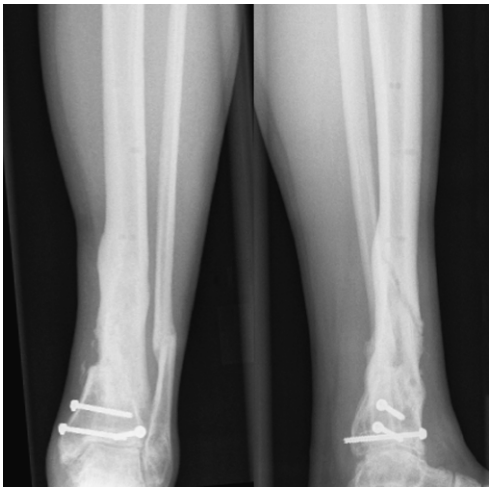

Fig. 1c

Radiographs showing a) a high-energy type-C2 fracture, b) treated by reconstruction of the joint line and external fixation, during which recombinant bone morphogenetic protein-7 was introduced into the fracture gap and over the proximal fracture, c) with healing by 20 weeks without further intervention.

in the tibia, diaphyseal extension, fixation of the associated fibular fractures, the closed or open nature of the fracture, the post-reduction displacement and the smoking habit of the patient. Details of both groups are given in Table I.

Data concerning the mechanism of injury, the OTA fracture classification, the grade of open fractures according to Gustilo and Anderson,[22] operative management and post-operative recovery were prospectively collected by the treating specialists on a dedicated form. Medication, body mass index and concomitant illnesses were identified from the patients' records. Data concerning smoking habits were obtained by personal interview.

The operative technique and later treatment were similar in the two groups. In OTA type-C fractures, reconstruction of the joint line was carried out first using minimally-invasive techniques, as described by Tornetta et al.[23] This was followed by the application of a two-ringed hybrid external fixator used as a neutralisation device (Ilizarov; Smith & Nephew, Memphis, Tennessee). Olive wires were used to secure the distal fragment and 5 mm half pins for the diaphyseal fragment (Table I).

In the BMP group the osteoinduction was stimulated with rhBMP-7 with bovine collagen as a carrier (Osigraft; Stryker Biotech, Limerick, Ireland), by applying the material into the fracture gap and over the proximal fracture line, at a mean of 18 days (5 to 47) from injury. One patient with multiple injuries with a high-energy open pilon fracture and a severe bony defect had two units of Osigraft mixed with cancellous autograft, and the other 19 received only one unit of Osigraft. The application time was dictated by the condition of the soft tissues. In type-C fractures the application was performed during the reconstruction and in type-A fractures it was done through a small incision at the site of the fracture. After application, the deep layers were closed with absorbable sutures and the wound was thoroughly washed with saline. The skin was closed with staples.

The bony defects were classified at the time of application of the external fixator according to the modified Wingquist-Hansen classification.[24] In one patient in the BMP group and in two in the matched group primary

Fig. 2a

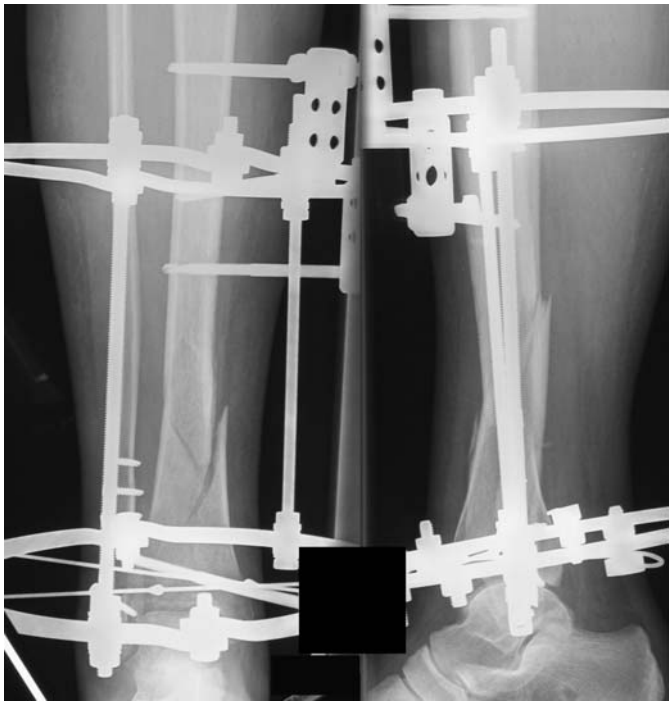

Fig. 2b

Fig. 2c

Radiographs showing a) a low-energy type-C1 fracture temporarily fixed by an external fixator bridging the ankle, b) then by a non-bridging external fixator without the use of recombinant bone morphogenetic protein-7. There were no clinical or radiological signs of union after three months, and c) finally, union at 24 weeks after cancellous autografting and internal fixation.

bone autografting was performed because of a metaphyseal bony defect.

Radiological measurements. Routine anteroposterior (AP) and lateral digital radiographs were used to measure the radiological parameters from post-reduction and follow-up films with PCView 1.2 DICOM 3.0 software (Jons-Finland Oy, Heinävesi, Finland). The measurements were made by the first author (JR). Displacement of the metadiaphyseal fracture was measured from the post-operative radiographs by the method described by Green and Gibbs.[25] In order to determine the translation on both AP and lateral radiographs, lines were drawn from the external cortices of the proximal and distal fragments to the level of the fracture. The degree of true

Table I. Clinical details of the 20 patients in each group

	BMP*	Matched	p-value
Mean age in years (range)	41.3 (23 to 79)	47.2 (28 to 78)	0.157
Men	11	10	> 0.9
Smokers	10	8	0.751
Multiple injuries	3	1	0.605
High-energy injury	10	11	> 0.9
Bone defects	6	3	0.451
Minor	4	2	
Moderate	1	1	
Severe	1	0	
Fibula intact or fibular fracture internally fixed	6	6	> 0.9
OTA† fracture type			> 0.9
A	7	7	
C	13	13	
Configuration of the metadiaphyseal fracture			0.57
Spiral	7	7	
Oblique	0	1	
Transverse	1	0	
Wedge	5	6	
Complex	7	6	
Tibial fractures with diaphyseal extension	4	4	> 0.9
Open fractures (all Type III-B)[22]	2	2	> 0.9
Number of distal wires			0.457
2	13	11	
3	7	8	
4	0	1	
Number of proximal half pins			> 0.9
2	11	12	
3	9	8	
Mean post-reduction displacement in mm (range)	2.3 (0 to 7)	1.7 (0 to 7)	0.142

* BMP, bone morphogenetic protein
† OTA, Orthopaedic Trauma Association

Table II. Outcome data for the 20 patients in each group

Outcome measure	BMP*	Matched	p-value
Mean time to union in weeks (range)	15.7 (7 to 43)	23.5 (11 to 63)	0.002
Mean duration of external fixation in weeks (range)	15 (9 to 37)	21.4 (10 to 40)	0.037
Mean length of sick leave in months (range)	6.3 (3 to 13)	9.0 (4 to 15)	0.018
Mean follow-up duration in months (range)	12 (11 to 13)	28 (12 to 45)	
Iowa ankle score[28]†	84 (70 to 100)	81.6 (46 to 98)	0.6
Excellent	5	7	
Good	10	6	
Fair	4	1	
Poor	0	4	
Restriction in range of movement			
Dorsiflexion (°)	12 (- 42 to 5)	10 (-33 to 6)	0.71
Plantar flexion (°)	13 (50 to 5)	7 (20 to 8)	0.3
Secondary intervention due to delayed healing	2	7	0.13

* BMP, bone morphogenetic protein
† one patient in the BMP group died before one year's follow-up and only 18 patients in the matched group were available for long-term follow-up

translation in mm was calculated according to the following formula:

$$\text{Translation} = \sqrt{\text{APtrans}^2 + \text{LATtrans}^2},$$

where APtrans is the translation measured from the AP radiograph and LATtrans is the translation measured from the lateral radiograph.

Assessment of union. This was assessed radiologically. All 40 sets of radiographs were read independently at one session by three of the authors (JR, ML and HP). Each was blinded to the interpretations given by the other assessors. All the assessors were instructed to define the fractures as united based on the presence of bridging callus at three of the four possible cortices and on the general appearance of the healing with trabecular bridging and remodelling such as to allow them to advise when the frame should be removed. In 18 cases (45%), all of the readers agreed. In 21 (52.5%), two of the surgeons agreed and the third's assessment did not differ by more than one month. In the latter cases, the time to union was defined by the two surgeons in agreement. In one case (2.5%), two surgeons agreed, but

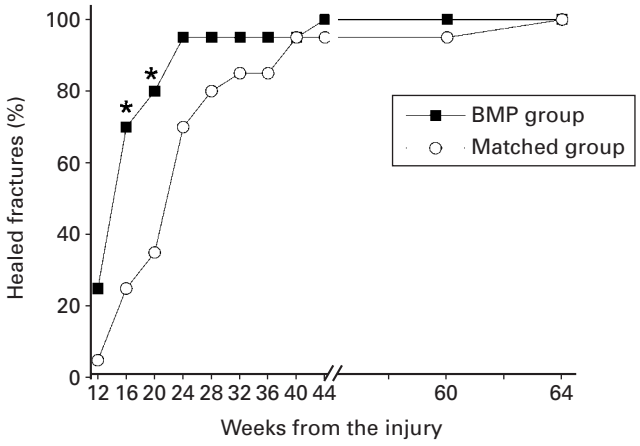

Fig. 3

The healing rates of the fractures in both groups (*, p < 0.05; BMP, bone morphogenetic protein).

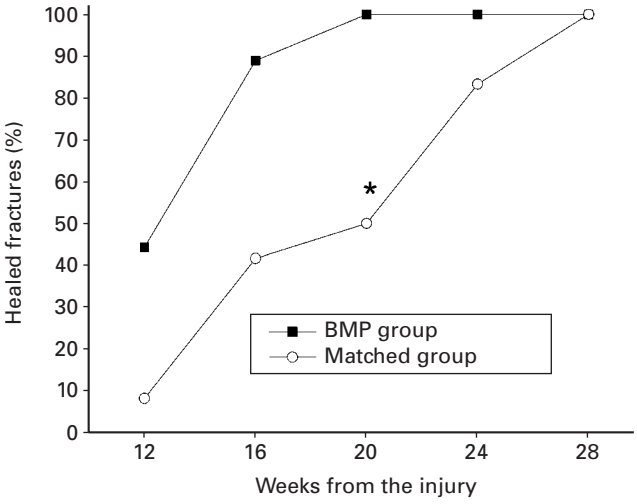

Fig. 4

The healing rates of the perfectly reduced fractures (displacement < 3 mm) without significant bony defects (*, p < 0.05; BMP, bone morphogenetic protein).

the third's assessment differed by two months. The radiographs were studied again in conference, with the third surgeon reaching agreement with the others. Union was defined as delayed when an additional operation was required to promote union.

Follow-up. The patients were reviewed monthly until the fracture had united. The patients in the BMP group had routine monthly visits for six months and again at one year for assessment of any adverse effects which might have resulted from the treatment, giving a mean follow-up of 12 months (11 to 13). In the matched group, 18 patients were further reviewed after a mean time of 28 months (10 to 54). One 72-year-old woman in the BMP group died from an unrelated cause six months after the injury. Her fracture had already united and the frame had been removed. At each visit radiographs were taken and adverse events were recorded. Clinical union and readiness for removal of the external fixator were defined by the treating surgeon as the absence of movement at the site of the fracture and the absence of pain on walking or when stress was applied to the fracture after removal of the connecting bars between the rings.

At the final review, the range of movement of the ankle was measured according to the method described by Lindsjo, Danckwardt-Lilliestrom and Sahlstedt.[26] Standing AP and lateral radiographs were taken of both legs, including both knees and subtalar joints. From these, the orientation of the joint line of the ankle was assessed by the method described by Paley.[27] The fracture was considered to be malunited if therex was at least a difference of 10° in either the anterior or the lateral distal tibial angle compared with that in the uninjured tibia. Functional recovery was assessed by the Iowa ankle score.[28] A score of 90 to 100 points was considered to be excellent, 80 to 89 points, good; 70 to 79 points, fair; and < 70 poor. There was no assessment of osteoarthritis in our study because of the short follow-up time in the BMP group. An independent physiotherapist performed the clinical tests.

Outcome measures. The evaluation of outcome was based on the time to radiological union of the fracture, the number of secondary interventions due to delayed healing, the duration of the application of the external fixator and the length of absence from work in those patients who were working at the time of injury.

Statistical analysis. This was performed by a statistician using SPSS statistical software (version 10.0.5; SPSS Inc., Chicago, Illinois). Continuous variables were reported as means and ranges. The chi-squared test and Fisher's exact test were used for univariate analysis of categorical data. The Wilcoxon signed-rank test was used to compare the healing times of the fractures and other continuous variables between groups, and the McNemar test to compare the number of healed fractures at different stages. Two-tailed p-values were reported with a p-value of ≤ 0.05 being considered significant. If a clinically significant reduction of unhealed fractures at a clinically relevant time point of 16 weeks is between 75% and 25%, 19 patients in each group are needed to show this in a case-controlled clinical study with a power of 80% ($\beta = 0.08$, $\alpha = 0.05$).

Results

All the fractures in both groups united. Outcome data are presented in Table II. The time taken to healing was significantly shorter in the BMP group than in the matched group ($p = 0.002$). Also, significantly more fractures had healed by 16 (14 *vs* 6; $p = 0.039$) and 20 weeks (16 *vs* 8; $p = 0.022$) in the BMP group than in the matched group respectively (Fig. 3). Accelerated healing was seen in perfectly reduced fractures without bone defects. Significantly more of these had healed by 20 weeks in the BMP group than in the matched group (9 of 9 *vs* 6 of 12; $p = 0.016$) (Fig. 4).

Table III. Data on patients who had delayed union requiring re-operation

	BMP* (n = 2)	Matched (n = 7)
Mean	1	2
Mean ages in years (range)	26 (23 to 29)	52 (44 to 78)
Smokers	2	3
OTA† fracture type		
A	0	3
C	2	4
Metadiaphyseal fracture		
Simple	0	5
Complex	2	2
Diaphyseal extension	2	1
Open fractures	2	2
Significant bone defects	2	1
Multiple injuries	2	1
Fibula intact or fracture fixed	2	4
Mean post-reduction displacement in mm (range)	1 (0 to 3)	4

* BMP, bone morphogenetic protein
† OTA, Orthopaedic Trauma Association

Secondary intervention due to delayed union was required for two patients in the BMP group and seven in the matched group (Table III). One of those in the BMP group, with an open fracture and a severe bony defect, had revision and introduction of antibiotic-impregnated beads as a spacer. After four weeks the defect was filled with an autogenous cancellous bone graft mixed with Osigraft. At six months a translucent line was still present at the metadiaphyseal junction. This disappeared after application of an additional unit of Osigraft. The other patient in the BMP group, with an open fracture and a moderate bony defect, had primary application of Osigraft without bone grafting, which in retrospect should have been undertaken. Autografting was performed at 14 weeks and the fracture subsequently united.

In the matched group, seven secondary interventions were needed. Six of these were relatively simple fractures with no bony defect (Fig. 2), while the remaining patient had a bony defect. This suggested that the risk for delayed union without stimulated osteoinduction was also high in patients with good reduction and/or no bony defect (Table III).

No significant differences were observed in the time to healing or secondary interventions between smokers and non-smokers in either the BMP ($p = 0.8$ and $p = 0.151$) or the matched group ($p = 0.791$ and 0.519), probably due to the relatively small number of cases. Of the 20 patients in the BMP group, ten were smokers, two of whom had delayed healing, but both had significant bony defects.

There were no deep infections in either group. Pin-track infections defined as discharge, redness, swelling and pain, and verified by bacterial culture were encountered in six patients in the BMP group and four in the matched group. In the BMP group one patient had three infected pin tracks. In the BMP group, all the infections resolved after local pin care and dressing changes and the administration of oral cefalexine (750 mg twice daily for seven days). One patient in the matched group had the frame and all five pins removed because of severe pin-track infection eight weeks after the injury, at which stage bridging callus was already present. The infection healed rapidly thereafter. In the BMP group, normal remodelling of the fracture had started at one year. In the BMP group one patient developed calcification of the soft tissues on follow-up radiographs, but without symptoms.

At the time of injury 16 patients in the BMP group and 13 in the matched group were employed. Of these, 14 and 12 respectively, regained their pre-injury employment. The length of absence from work ($p = 0.018$) and the duration of the external fixation ($p = 0.037$) were significantly longer in the matched group than in the BMP group (Table II).

No significant differences were found between the groups in the mean Iowa ankle scores ($p = 0.6$) or in the reduction in range of movement of the ankle (dorsiflexion $p = 0.71$, plantar flexion $p = 0.3$; Table II). There was malunion of two fractures in each group. A corrective osteotomy was done in one patient in the BMP group. The other patient in the BMP group and both in the matched group did not want further surgery.

Discussion

Osteoinduction with rhBMP-7 significantly accelerated the healing of distal tibial fractures which were treated by external fixation. This finding is in line with observations on the effect of rhBMP-2 on open tibial fractures treated by intramedullary nailing,[29] and also with the results of an experimental study on tibial fractures in goats treated by external fixation.[13] Together these findings suggest that rhBMP-2 and rhBMP-7 can accelerate the healing of fresh fractures. However, this was not shown by the study of Maniscalco et al[30] in which no difference was found in the time to healing of seven tibial fractures treated with rhBMP-7 and external fixation and of seven treated by external fixation alone.

Our study is the first clinical survey in which rhBMP-7 has been applied to distal tibial fractures. Previous studies have shown that these fractures can have major complications, of which infected nonunion is one of the most difficult to treat.[1,2,31] External fixation gives acceptable

functional results with fewer complications compared with traditional plating.[32,33] However, external fixation of tibial fractures is often associated with delayed healing.[34] A high rate of primary or late bone grafting is usually required to promote union.[2-4,32]

Although metaphyseal fractures usually heal quickly, there are two main reasons why distal tibial fractures treated by external fixation heal slowly; limited muscle cover and a gap between the fracture fragments. In an earlier study on distal tibial fractures we showed that external fixation often left a gap > 3 mm between the fragments and that this was the main cause of delayed union and secondary interventions.[35]

The mechanism by which BMPs accelerate the union of fresh fractures is not completely understood. It is generally known that the main action of BMPs is to promote the differentiation of mesenchymal cells to osteoblastic cells, but there is only marginal evidence to show that this process can be accelerated by BMPs in fresh fractures. Initially, we assumed that the accelerated healing of the fracture was caused by the ability of rhBMP-7 to bridge critically-sized defects, and was not due to a direct effect on bone healing. RhBMP-7 is known to be able to bridge defects of long bones.[18] However, when we analysed separately the perfectly reduced fractures without any bony defects, we found that accelerated healing occurred in these cases as well. Accordingly, it seems that rhBMP-7 may have a direct action on bone healing by accelerating the differentiation of stem cells into osteoblasts. In addition, Ramoshebi and Ripamonti[36] have shown that BMP-7 stimulates angiogenesis which may improve the initial induction of bone formation in fractures which have been compromised by insufficient blood supply and poor soft-tissue cover.

The timing of the application of rhBMP may be important. Experimental animal studies have shown that BMP-7 has a restricted period of expression from day 14 to day 21 of fracture healing.[37] Cheng et al[38] suggested that BMP-2, -6 and -9 may be the most potent for inducing osteoblastic differentiation of mesenchymal progenitor cells, while BMP-7 can stimulate osteogenesis in mature osteoblasts. RhBMP-7 was applied in our series at a mean time of 18 days from the injury, a stage at which BMP-7 is normally expressed. It may be that rhBMP-7 may not produce a similar effect if it is applied earlier.

In a recent study, Watson et al[39] suggested that complications, especially delayed union of distal tibial fractures, should be prevented by primary osteoinduction using autogenous cancellous bone grafting. On the other hand, the soft-tissue cover over the distal tibia is limited, and bulky autogenous bony material may encourage wound dehiscence and infection. In randomised clinical studies rhBMP-7 was comparable to autogenous bone grafting in stimulating bone growth.[15,17] In a study by Friedlander et al,[17] autograft bone was compared with rhBMP-7 in the treatment of nonunion. The risk of infection at the site of implantation was significantly lower in the rhBMP-7 group. Early stimulation of bone formation at the site of the fracture gives increased stability of the fracture and is important in reducing infection.[40] Thus, the application of a small volume of rhBMP-7 in distal tibial fractures with the avoidance of the complications associated with the harvest of bone graft is attractive. Friedlander et al[17] found that 20% of the patients in their autografting group had chronic pain at the donor site.

It is noteworthy that some patients in the matched group without significant bony defects required a secondary intervention, while none in the BMP group did. This may indicate that all patients with distal tibial fractures should have osteoinduction with either autogenous cancellous bone graft or BMP. A disadvantage of the method described here is that an additional incision is needed to apply rhBMP-7 in those fractures which would not otherwise need an open procedure, i.e. type-A fractures. This may be a potential risk for wound infection.

Secondary interventions were required in two patients in the BMP group for delayed healing. Both had significant bony defects. In a study by Watson, Anders and Moed[41] on tibial fractures with bone loss which had been treated by external fixation, 40% needed at least one additional bone grafting procedure for union to be obtained. It seems that in cases of massive bony defects, a BMP implant alone is not sufficient, but should be combined with bone grafting. In contrast, four fractures with minor bony defects in the BMP group in the present study healed without additional measures indicating that rhBMP-7 with carrier may be sufficient to heal wedge-type (> 50% but < 100%) defects of less than 2 cm in length.

We used radiological evaluation of union because of the possible variability in the clinical assessment of union. Radiological union is based on the determination of the number of cortices bridged by callus and the surgeon's general assessment and has been shown to be a reliable and reproducible method.[42]

There were no statistically significant differences in the clinical scores between the groups, but four patients had a poor ankle score in the matched group with none in the BMP group, although the follow-up time was shorter in the latter. It is known that in pilon fractures functional results improve for a mean of 2.4 years after injury.[43]

Although our study was not randomised, we believe that the findings are not biased by the selection of the patients. The control group of 47 patients from whom the matched group was selected was a consecutive series of patients with distal tibial fractures who had been treated by two-ring hybrid external fixation. Those in the BMP group represented the next 20 consecutive patients who had been treated similarly except for the application of rhBMP-7. The background and treatment data of the matched groups were sufficiently uniform.

In Finland, primary hospital costs account on average for only 13% of the total economic burden caused by injuries, the main burden being indirect costs and lost working days.[44] Here, the use of rhBMP-7 shortened absence from work by a mean of almost three months. This indicates that

this treatment, despite the high price of the implant, is cost-effective. Based on the findings from this and our previous study,[35] osteoinduction with rhBMP-7 is beneficial in pilon fractures with significant metaphyseal comminution and also in simple fractures, in which post-reduction radiographs show residual displacement of more than 3 mm.

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

1. **McFerran MA, Smith SW, Boulas HJ, Schwartz HS.** Complications encountered in the treatment of pilon fractures. *J Orthop Trauma* 1992;6:195-200.
2. **Wyrsch B, McFerran MA, McAndrew M, et al.** Operative treatment of fractures of the tibial plafond: a randomized, prospective study. *J Bone Joint Surg [Am]* 1996;78-A:1646-57.
3. **Anglen JO.** Early outcome of hybrid external fixation for fracture of the distal tibia. *J Orthop Trauma* 1999;13:92-7.
4. **Pugh KJ, Wolinsky PR, McAndrew MP, Johnson KD.** Tibial pilon fractures: a comparison of treatment methods. *J Trauma* 1999;47:937-41.
5. **Cook SD, Rueger DC.** Osteogenic protein-1: biology and applications. *Clin Orthop* 1996;324:29-38.
6. **Matthews SJ.** Biological activity of bone morphogenetic proteins (BMP's). *Injury* 2005;3(Suppl 3):34-7.
7. **Einhorn TA.** Clinical applications of recombinant human BMPs: early experience and future development. *J Bone Joint Surg [Am]* 2003;85-A(Suppl 3):82-8.
8. **Termaat MF, De Boer FC, Bakker FC, Patka P, Haarman HJ.** Bone morphogenetic proteins: development and clinical efficacy in the treatment of fractures and bone defects. *J Bone Joint Surg [Am]* 2005;87-A:1367-78.
9. **Cook SD, Patron LP, Salkeld SL, Rueger DC.** Repair of articular cartilage defects with osteogenic protein-1 (BMP-7) in dogs. *J Bone Joint Surg [Am]* 2003;85-A(Suppl 3):116-23.
10. **Cook SD, Salkeld SL, Patron LP, Sargent MC, Rueger DC.** Healing course of primate ulna segmental defects treated with osteogenic protein-1. *J Invest Surg* 2002;15:69-79.
11. **Hyun SJ, Han DK, Choi SH, et al.** Effect of recombinant human bone morphogenetic protein-2, -4, and -7 on bone formation in rat calvarial defects. *J Periodontol* 2005;76:1667-74.
12. **Welch RD, Jones AL, Bucholz RW, et al.** Effect of recombinant human bone morphogenetic protein-2 on fracture healing in a goat tibial fracture model. *J Bone Miner Res* 1998;13:1483-90.
13. **de Boer FC, Bramer JA, Blokhuis TJ, et al.** Effect of recombinant human osteogenic protein-1 on the healing of a freshly closed diaphyseal fracture. *Bone* 2002;31:158-64.
14. **Grauer JN, Vaccaro AR, Kato M, et al.** Development of a New Zealand white rabbit model of spinal pseudarthrosis repair and evaluation of the potential role of OP-1 to overcome pseudarthrosis. *Spine* 2004;29:1405-12.
15. **Johnsson R, Stromqvist B, Aspenberg P.** Randomized radiostereometric study comparing osteogenic protein-1 (BMP-7) and autograft bone in human noninstrumented posterolateral lumbar fusion. *Spine* 2002;27:2654-61.
16. **Vaccaro AR, Anderson DG, Patel T, et al.** Comparison of OP-1 Putty (rhBMP-7) to iliac crest autograft for posterolateral lumbar arthrodesis: a minimum 2-year follow-up pilot study. *Spine* 2005;30:2709-16.
17. **Friedlander GE, Perry CR, Cole JD, et al.** Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions. *J Bone Joint Surg [Am]* 2001;83-A(Suppl 1):151-8.
18. **Geesink RG, Hoefnagels NH, Bulstra SK.** Osteogenic activity of OP-1 bone morphogenetic protein (BMP-7) in a human fibular defect. *J Bone Joint Surg [Br]* 1999;81-A:710-18.
19. **Patel TC, Erulkar JS, Gruaer JN, et al.** Osteogenic protein-1 overcomes the inhibitory effect of nicotine on posterolateral lumbar fusion. *Spine* 2001;26:1656-61.
20. **McKee MD, Schemitsch EH, Waddell JP, et al.** The effect of human recombinant bone morphogenetic protein (rhBMP-7) on the healing of open tibial shaft fractures: results of a multi-center, prospective, randomized clinical trial. *Procs Annual Meeting American Academy of Orthopaedic Surgeons*, 2003.
21. **Müller ME, Nazarian S, Koch P, Schatzker J.** *The comprehensive classification of fractures of long bones*. New York: Springer, 1990.
22. **Gustilo RB, Anderson JT.** Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective and prospective analyses. *J Bone Joint Surg [Am]* 1976;58-A:453-8.
23. **Tornetta P 3rd, Weiner L, Bergman M, et al.** Pilon fractures: treatment with combined internal and external fixation. *J Orthop Trauma* 1993;7:489-96.
24. **Robinson CM, McLaughland G, Christie J, McQueen MM, Court-Brown CM.** Tibial fractures with bone loss treated by primary reamed intramedullary nailing. *J Bone Joint Surg [Br]* 1995;77-B:906-13.
25. **Green SA, Gibbs P.** The relationship of angulation to translation in fracture deformities. *J Bone Joint Surg [Am]* 1994;76-A:390-7.
26. **Lindsjo U, Danckwardt-Lilliestrom G, Sahlstedt B.** Measurement of the motion range in the loaded ankle. *Clin Orthop* 1985;199:68-71.
27. **Paley D.** Normal lower limb alignment and joint orientation. In: Paley D, ed. *Principles of deformity correction*. Berlin: Springer-Verlag, 2002:8-9.
28. **Merchant TC, Dietz FR.** Long-term follow-up after fractures of the tibial and fibular shafts. *J Bone Joint Surg [Am]* 1989;71-A:599-606.
29. **Govender S, Csimma C, Genant HK.** Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of our hundred and fifty patients. *J Bone Joint Surg [Am]* 2002;84-A:2123-34.
30. **Maniscalco P, Gambera D, Bertone C, et al.** Healing of fresh tibial fractures with OP-1: a preliminary report. *Acta Biomed Parmense* 2002;73:27-33.
31. **Teeny SM, Wiss DA.** Open reduction and internal fixation of tibial plafond fractures: variables contributing to poor results and complications. *Clin Orthop* 1993;292:108-17.
32. **Bone L, Stegemann P, McNamara K, Seibel R.** External fixation of severely comminuted and open tibial pilon fractures. *Clin Orthop* 1993;292:101-7.
33. **Marsh JL, Bonar S, Nepola JV, Decoster TA, Hurwitz SR.** Use of an articulated external fixator for fractures of the tibial plafond. *J Bone Joint Surg [Am]* 1995;77-A:1498-509.
34. **Court-Brown CM.** Fractures of the tibia and fibula. In: Buckholz RW, Heckman JD, eds. *Rockwood and Green's fractures in adults*. Fifth ed. Philadelphia: JB Lippincott Company, 2001:1939-2000.
35. **Ristiniemi J, Flinkkilä T, Hyvönen P, et al.** Two ring hybrid external fixation of distal tibial fractures: a review of 47 cases. *J Trauma* 2007;62:174-83.
36. **Ramoshebi LN, Ripamonti U.** Osteogenic protein-1, a bone morphogenetic protein, induces angiogenesis in the chick choriollantoic membrane and synergizes with basic fibroblast growth factor and transforming growth factor-beta 1. *Anat Rec* 2000;259:97-107.
37. **Cho TJ, Gerstenfeld LC, Einhorn TA.** Differential temporal expression of members of the transforming growth factor beta superfamily during murine fracture healing. *J Bone Miner Res* 2002;17:513-20.
38. **Cheng H, Jiang W, Phillips FM, et al.** Osteogenic activity of the fourteen types of human bone morphogenetic proteins (BMPs). *J Bone Joint Surg [Am]* 2003;85-A:1544-52.
39. **Watson JT, Kanges DE, Cramer KE, Moed BR.** Analysis of failure of hybrid external fixation techniques for the treatment of distal tibial pilon fractures. *Procs OTA meeting*, 2000.
40. **Worlock P, Slack R, Harvey L, Mawhinney R.** The prevention of infection in open fractures: an experimental study of the effect of fracture stability. *Injury* 1994;25:31-8.
41. **Watson JT, Anders M, Moed BR.** Management strategies for bone loss in tibial shaft fractures. *Clin Orthop* 1995;315:138-52.
42. **Whelan DB, Bhandari M, McKee MD, et al.** Interobserver and intraobserver variation in the assessment of the healing of tibial fractures after intramedullary fixation. *J Bone Joint Surg [Am]* 2002;84-A:15-18.
43. **Marsh JL, Weigel DP, Dirschl DR.** Tibial plafond fractures: how do these ankles function over time? *J Bone Joint Surg [Am]* 2003;85-A:287-95.
44. **Vuoriainen T, Helenius M, Heikkila J, Olkkonen S.** Falling accidents of pedestrians and cyclists in Espoo, Helsinki, Jyväaskylä and Oulu (Finnish National Road Administration Series 48/2000). http://alkotiehallininfo.fi/kulkaisot/pdf/3200634.pdf (Date last accessed March 27th 2001).