Recombinant human bone morphogenetic protein-2 for grade III open segmental tibial fractures from combat injuries in Iraq

T. R. Kuklo,
A. T. Groth,
R. C. Anderson,
H. M. Frisch,
R. B. Islinger

From Walter Reed Army Medical Centre, Washington DC, USA

This is a retrospective consecutive case series of 138 Gustillo-Anderson type IIIB and IIIC segmental tibial fractures treated at Walter Reed Army Medical Center in soldiers injured in Iraq between March 2003 and March 2005. Five patients with a head injury and four who were lost to follow-up were excluded. The patients were treated definitively with either a ringed external fixator or a reamed intramedullary nail, evaluated in terms of supplementary bone grafting with either autogenous bone (group 1, 67 patients) or recombinant human bone morphogenetic protein-2 at 1.50 mg/ml applied to an absorbable collagen sponge (group 2, 62 patients).

The mechanism of injury, defect size and classification, associated injuries, presence of infection, preliminary treatment/fixation, number of procedures before definitive management, time to and details of definitive management, subsequent infection, re-operation, smoking history and other complications were noted. Radiographs were assessed for union, delayed union or nonunion by an independent investigator.

All the patients were male. Their mean age was 26.6 years (20 to 42) and the mean follow-up was for 15.6 months (12 to 32). Group 2 had a slightly higher profile of concomitant injuries and a slightly worse fracture classification, but these were not significant.

The rate of union was 76% (51 of 67) for group 1 and 92% for group 2 (57 of 62; $p = 0.015$). There was also a higher rate of subsequent infection in group 1 (14.9%) compared with group 2 (3.2%; $p = 0.001$) and a higher rate of re-operation (28%) in group 1 ($p = 0.003$). There were no observed hypersensitivity reactions to the recombinant human bone morphogenetic protein-2 implant.

T. R. Kuklo, MD, JD, Associate Professor
Washington University School of Medicine, 660 S. Euclid, St. Louis, Missouri 63110, USA.

A T. Groth, MD, Orthopaedic Surgeon
R. C. Anderson, MD, Orthopaedic Surgeon
H. M. Frisch, MD, Orthopaedic Surgeon
R. B. Islinger, MD, Orthopaedic Surgeon
Department of Orthopaedics and Rehabilitation
Walter Reed Army Medical Center, Washington DC, 20307, USA.

Correspondence should be sent to Professor T. R. Kuklo at One Barnes-Jewish Hospital Plaza, Suite 11300 West Pavilion, St. Louis, Missouri 63110, USA; e-mail: kuklot@wustl.edu

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In the recent war in Iraq, as in previous conflicts, injuries to the musculoskeletal system account for more than 70% to 80% of injuries.[1-11] In Iraq, penetrating injuries were more frequently secondary to a blast effect from incendiary explosive devices, exploding ordinance or makeshift artillery and landmines, as opposed to gunshot wounds. Owing to the high level of kinetic energy from these devices, there is a large zone of injury, with severe soft-tissue damage, massive bone loss and significant contamination from dirt, clothing, fragmented missiles and various other foreign materials.

The injuries include open tibial fractures, which are widely regarded as having an unacceptably high rate of delayed and nonunion, as well as significant morbidity, even in non-military injuries.[12,13] For Gustillo and Anderson[14] type III fractures, a delayed rate of union as high as 43% to 100% has been reported by various authors, but in modern practice, this rate is probably somewhat less.[12,14-18] For wartime injuries, the rates may be higher due to high-velocity and blast injuries,[1,2] in which the area of injury is extensive and often difficult to appreciate completely on initial evaluation.

Throughout several past conflicts, although improvements in medical evacuation have resulted in a significant reduction in mortality on the battlefield, there has been an accompanying increase in morbidity. Soldiers with multiple limb, and/or other injuries, are typically evacuated from the war zone through fixed military hospitals. Initial assessment and stabilisation, wound evaluation, debridement, irrigation and stabilisation, generally with an external fixator, are performed in the war zone at a Combat Support Hospital or equivalent. Evacuation is followed by transport to the United States, typically within two to ten days. General antibiotic prophylaxis is continued routinely. Complete assessment of the extent of injury and fracture characteristics, mechanism of injury, soft-tissue viability and degree of bacterial contamination is

Table I. Tibial fracture classification and rate of union from combat injuries in Iraq

	Total	Grade*		Patients with a head injury	Lost to follow-up	Union (%)†	Post-operative infections (rate) (%)
		IIIB	IIIC				
Group 1							
Autologous bone graft	73	62 (2)	11 (1)	3	3	51/67 (*76*)‡	10 (*14.9*)§
Group 2							
rhBMP-2¶	65	51 (2)	14	2	1	57/62 (*92*)‡	2 (*3.2*)§
Total	138	113 (4)	25 (1)	5	4	108/129 (*84*)	12 (*9.3*)

* includes patients with an injury in parentheses, who were not included in the analysis

†, does not include patients lost to follow-up or with a head injury

‡, $p = 0.015$

§, $p = 0.001$

¶ rhBMP-2, recombinant human bone morphogenetic protein-2

repeated at the tertiary hospital. Because of the delay, presentation can vary considerably.

With advances in medical and surgical treatment, severe open fractures which hitherto were treated routinely by amputation can be now managed using complex reconstructive techniques.[19,20] The extent of injury and the expectations of patients and society in general have accelerated the use of emerging technologies such as recombinant human bone morphogenetic protein-2 (rhBMP-2) (InFUSE, Medtronic Sofamor Danek, Memphis, Tennessee) for severe open tibial fractures.

The purpose of this retrospective study was to compare the management of Gustillo-Anderson type IIIB and IIIC segmental tibial fractures from Iraq treated with autologous bone grafting or rhBMP-2 in relation to subsequent infection, reoperation and fracture union.

Patients and Methods

Between March 2003 and March 2005, 138 Gustilo-Anderson type IIIB and IIIC segmental tibial fractures in 138 soldiers returning from Iraq were treated at the Walter Reed Army Medical Centre. Five patients with a head injury were excluded and four were lost to follow-up leaving 129 patients in the study. All were male, with a mean age of 26.6 years (20 to 42) and a mean follow-up of 15.6 months (12 to 32). The protocol was approved by the Institutional Review Board and informed consent was obtained from all patients for specific fracture management, including the off label use of rhBMP-2. Patients were treated with a ringed fixator or reamed intramedullary nail and evaluated retrospectively in terms of supplementary bone grafting with autologous bone (67 patients, group 1) or rhBMP-2 (62 patients, group 2). Treatment was determined by the attending surgeon on a case-by-case basis (Table I). A segmental defect was considered as greater than 50% circumferential bone loss more than 1 cm.

The medical records, radiographs and wound photographs were reviewed in all cases to confirm fracture grade and any associated neurovascular injury. Initial operation records were reviewed to establish the Gustilo-Anderson fracture grade. Demography also included the mechanism of injury, defect size and classification, associated injuries, presence of infection, preliminary treatment/fixation, number of procedures before definitive management, time to and details of definitive management, smoking history, subsequent infection, reoperation and other complications.

Injury severity scoring, such as the Mangled Extremity Score[21] or the Sickness Impact Profile,[22] was not routinely used, as we found these not to be effective management tools.

Anteroposterior and lateral radiographs were classified by an independent observer (ATG) as union or nonunion (an absence of bridging bone), with delayed union at 12 months considered as nonunion.

Repeated debridement and irrigation was performed routinely and there was a mean of 4.5 preliminary procedures (2 to 14), usually two to four days apart, before definitive management. Occasionally a particular wound may initially require daily debridement. Antibiotic beads and/or vacuum-assisted closure, a closed negative-pressure system (Kinetic Concepts Incorporated, San Antonio, Texas) for open wound management set at 50 mmHg to 75 mmHg continuous suction, were used routinely.

The initial fracture management involved either a unilateral external fixator (Hoffman II External Fixator, Howmedica Stryker Osteonics, Allendale, New Jersey) or splinting. Definitive management involved either a circular or hybrid external fixator, or a locked intramedullary nail. The preferred site for autogenous bone graft was the ipsilateral iliac crest. Soft-tissue cover, such as local fasciocutaneous flaps or muscle flaps and skin grafting, was performed at the definitive operation (Table II) according to

Table II. Preliminary and definitive fracture fixation*

	Group 1 (n = 67)	Group 2 (n = 62)
Preliminary fixation		
Splint	1	2
External fixator	66	60
Definitive fixation		
External fixator	13	12
Ringed external fixator	6	10
Intramedullary nail	48	40
Fasciocutaneous flaps	3	2
Pedicled muscle flaps	28	23

* does not include patients with head injury or those lost to follow-up

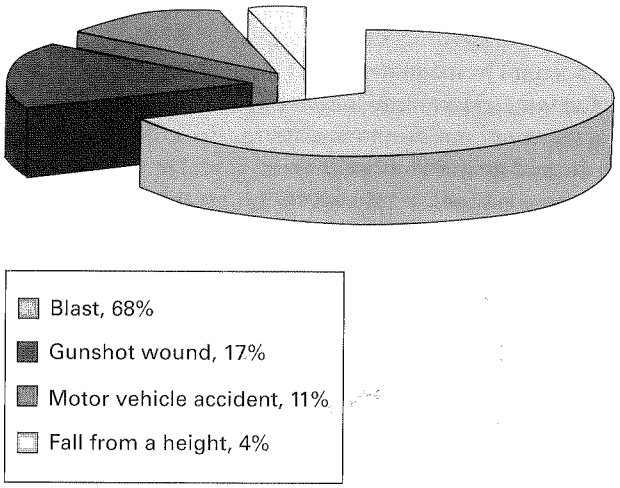

Fig. 1

Pie chart showing the mechanism of injury.

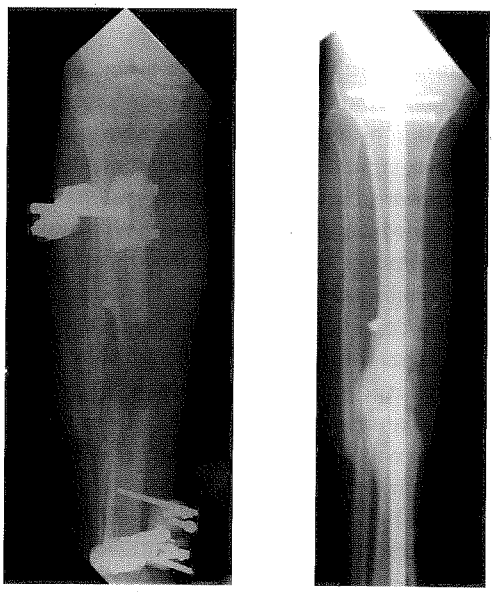

Fig. 2a

Fig. 2b

Initial anteroposterior radiographs a) of a type IIIB tibial fracture in a 40-year-old man who sustained a gunshot wound in Iraq and b) 36-weeks post-operatively showing tibial union after bone grafting with corticocancellous allograft and recombinant human bone morphogenetic protein-2.

the overall condition of the patient, assessment of other injuries and wound status. Antibiotic cover was generally continued for 48 to 72 hours post-operatively.

rhBMP-2 was implanted on an absorbable type-I collagen sponge (ACS, bovine tendo Achillis, Medtronic Sofamor Danek), which delivers rhBMP-2 and resorbs within a reasonable time.[23-31] The intra-operative preparation of the implant has been well described.[32] The concentration was 1.50 mg/ml, as recommended by the manufacturer, with a total dose of 12 mg in all applications (one large kit), except for one patient with a 12 cm segmental defect in whom two large kits (24 mg) of rhBMP-2 were used. The 'bulking agent' varied from cancellous allograft bone chips earlier in the war to a corticocancellous allograft bone mixture (primarily a 70%:30% mix) as experience was gained. Although it was agreed that there were no significant differences between the techniques, it was generally thought that the corticocancellous mixture remodelled more slowly and so it became the preferred technique.

If a drain was used, it was placed away from the rhBMP-2 to minimise any potential leaching. Vacuum-assisted closure was used routinely following local muscle flaps and split-thickness skin grafts in both groups. It was left in place for three to five days at 50 mmHg to 75 mmHg with elevation of the leg and non-weight-bearing. After this, weight-bearing was determined according to the stability of the fracture and the type of fixation. Patients with external fixators were allowed partial weight-bearing, and those with ringed fixators or intramedullary nails were able to bear weight as tolerated. Radiographs were taken routinely

Table III. Secondary intervention rate

	Patients who had further surgery (%)	Additional procedures	p-value
Group			
1 (n = 67)	19 (*28*)	37	0.003
2 (n = 62)	5 (*8*)	6	
Total (n = 129)	24 (*19*)	43	

at two weeks, six weeks, three months, six months and 12 months post-operatively when possible.

Standard demographic statistics and means were determined and comparisons between groups evaluated with a chi-squared test.

Results

The groups were equivalent in terms of age (group 1: mean 25.7 years, (20 to 39); group 2: mean 26.8 years, 20 to 42), mechanism of injury (Fig. 1) and defect size. In terms of infection or positive wound culture on arrival at the tertiary centre, the overall infection or severe colonisation rate was 69%, and there were no differences between the groups. At the beginning of the conflict, all wounds were cultured repeatedly; however, this policy changed because it was not proven as a definitive management tool. Nevertheless, internal fixation was not undertaken unless the clinical appearance of the wound and cultures indicated that the environment was free of infection.

There was no statistically significant difference between the groups in terms of initial or definitive fixation, or soft-tissue management ($p > 0.05$, Table II). The number of operations before definitive fixation varied greatly between two and 14 but did not differ between the groups. A total of 14 patients (11%) were smokers, eight in group 1 and six in group 2, which was not significant. Although three of eight smokers (38%) in group 1 and three of six (50%) in group 2 were considered to have a nonunion, the numbers were too small for statistical analysis.

Group 2 had more concomitant injuries and a slightly worse fracture classification but these were not significant ($p > 0.05$). There were no clinically apparent hypersensitivity reactions to rhBMP-2.

There were 51 pedicled muscle flaps and five fasciocutaneous flaps (equally divided between the two groups), none of which failed, although six required dressing changes for minor edge necrosis. No patient required amputation secondary to chronic infection or nonunion.

On radiological analysis, the rate of union was 76% for group 1 (51 of 67) for group 1 and 92% for group 2 (57 of 62, $p = 0.015$, Fig. 2). If those lost to follow-up were analysed on a worst-case scenario or intention-to-treat basis, the rate of union would be 73% (51 of 70) for group 1 and 90% (57 of 64) for group 2 ($p = 0.014$). Also, there was a higher rate of subsequent infection in group 1 (ten patients, 14.9%; three infected nonunions) than in group 2 (two patients, 3.2%; one infected nonunion, $p = 0.001$). Repeated debridement was required in all cases and repeated procedures in several patients. Consequently, 19 of 67 patients (28%) in group 1 (37 procedures) and five of 62 patients (8%) in group 2 required an additional procedure (six procedures, $p = 0.003$). This is equivalent to 0.55 additional procedures per patient in group 1 and 0.10 in group 2 (Table III).

Discussion

As ever, open tibial fractures sustained in wartime remain a complex and challenging problem. Our general approach to all of these fractures included aggressive and repeated debridement and irrigation to establish a clean, stable wound suitable for stabilisation with instrumentation, bone grafting and soft-tissue defect management as needed.

This retrospective consecutive case series is the largest reported. Owing to the consistency of the evacuation system and the large number of patients at a single institution, it provides an excellent means of evaluating the effectiveness of rhBMP-2. Although treatment was determined by the attending surgeon, the two groups are equivalent in terms of demography, mechanism of injury, defect size and classification, concomitant injuries, presence of infection/positive wound culture, preliminary treatment/fixation, number of procedures before definitive management, time to definitive management and details thereof, soft-tissue management and smoking history.

Whereas previous studies of tibial fractures variably report significant delays in healing and overall lower union rates than in other long bones, improved results are reported with aggressive soft-tissue management and the use of intramedullary fixation when possible,[17,31-34] which has also been our standard approach.

The overall rate of union of 84% is consistent with similar previously reported series of type III fractures.[35-38] However, those primarily included type IIIB fractures and the injury profile in this series is slightly more severe owing to our inclusion of type IIIC fractures. Even so, the 92% rate of union in group 2 patients is a striking finding, as was a much lower infection rate. The reported infection rate in type III fractures is generally reported to be between 14% and 20%.[17,38,39] Our overall infection rate of 9.3% is slightly lower, and very similar for group 1 (14.9%). This acceptable rate is probably due to the careful, repeat debridements before definitive treatment. However, group 2 had a strikingly lower infection rate

(3.2%), which we believe is directly attributable to rhBMP-2, one of its properties being angiogenesis. This ability to increase the vascularity of the injury site is most likely the major difference in our series, but this does not imply that meticulous debridement is not necessary.

This series is not ideal, as it is a retrospective review of a series of various open tibial fractures. However, in this setting, a prospective randomised trial might be considered to be unethical and impossible because of multiple confounding variables. In the circumstances, as each soldier was treated using similar algorithms in the evacuation, initial care and subsequent management of these injuries, we believe it is a good method of reviewing the clinical use of advanced bone grafting technologies.

Every publication or discussion on emerging technologies centres on the additional cost of such intervention. In this series, all care was given at a United States military hospital, and therefore, pre-certification and insurance reimbursement are not foremost, especially in the care of wounded soldiers. Nevertheless, there is a compelling argument for the continued use of such technologies, as the primary outcome measures of union, rate of infection, and reoperation were all improved with rhBMP-2. These results should therefore be considered in the management of similar non-combat injuries but a cost-benefit analysis was beyond the cope of this study.

In conclusion, the use of rhBMP-2 for Gustilo-Anderson type IIIB and IIIC segmental tibial fractures in soldiers from Iraq resulted in an improved rate of union, a reduced rate of infection, and a subsequent 28% decrease in the rate of reoperation.

Supplementary Material

A further opinion by Mr G. Bowyer is available with the electronic version of this article on our website at www.jbjs.org.uk

References

1. **Bajec J, Gang RK, Lari AR.** Post gulf war explosive injuries in liberated Kuwait. *Injury* 1993;24:517-20.
2. **Bartlett CS, Helfet DL, Hausman MR, Strauss E.** Ballistic and gunshot wounds: effects on musculoskeletal tissues. *J Am Acad Orthop Surg* 2000;8:21-36.
3. **Batinica J, Batinica S.** War wounds in the Sibenik area during the 1991-1999 war against Croatia. *Mil Med* 1995;160:124-8.
4. **Bowyer GW, Cooper GJ, Rice P.** Management of small fragment wounds in war: current research. *Ann R Coll Surg Engl* 1995;77:131-4.
5. **Burkle FMJM, Newland C, Meister SJ, Blood CG.** Emergency medicine in the Persian Gulf War. part 2: battlefield casualties. *Ann Emerg Med* 1994;23:755-60.
6. **Covey DC, Lurate RB, Hatton CT.** Field hospital treatment of blast wounds of the musculoskeletal system during the Yugoslav civil war. *J Orthop Trauma* 2000;14:278-86.
7. **Islinger RB, Kuklo TR, McHale KA.** A comparison of orthopaedic injuries in three recent United States military conflicts. *Mil Med* 2000;165:463-5.
8. **Jackson DS, Batty CG, Ryan JM, McGregor WS.** The Falklands War: Army field surgical experience. *Ann R Coll Surg Engl* 1983;65:281-5.
9. **Jevtic M, Petrovic M, Ignjatovic D, et al.** Treatment of wounded in the combat zone. *J Trauma* 1996;40(3 Suppl):173-6.
10. **Rowley DI.** The management of war wounds involving bone. *J Bone Joint Surg [Br]* 1996;78-B:706-9.
11. **Uhorchak JM, Arciero RA.** Recent wounds of war: lessons learned and relearned. *Tech Orthop* 1995;10:176-88.
12. **Riemer BL, DiChristina DG, Cooper A, et al.** Nonreamed nailing of tibial diaphyseal fractures in blunt polytrauma patients. *J Orthop Trauma* 1995;9:66-75.
13. **Edwards CC, Simmons SC, Browner BD, Weigel MC.** Severe open tibial fractures: results treating 202 injuries with external fixation. *Clin Orthop* 1988;230:98-115.
14. **Gustilo RB, Anderson JT.** Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective prospective analysis. *J Bone Joint Surg [Am]* 1976;58-A:453-8.
15. **Gustilo RB, Mendoza RM, Williams DN.** Problems in the management of type III (severe) open fractures: a new classification of type III open fractures. *J Trauma* 1984;24:742-6.
16. **Caudle RJ, Stern PJ.** Severe open fractures of the tibia. *J Bone Joint Surg [Am]* 1987;69-A:801-7.
17. **Sanders R, Jersinovich I, Anglen J, DiPasquale T, Herscovici D Jr.** The treatment of open tibial shaft fractures using an interlocked intramedullary nail without reaming. *J Orthop Trauma* 1994;8:504-10.
18. **Naique B, Pearse M, Nanchahal J.** Management of severe open tibial fractures: the need for combined orthopaedic and plastic surgical treatment in specialist centres. *J Bone Joint Surg [Br]* 2006;88-B:351-7.
19. **Hansen ST Jr.** The type-IIIC tibial fracture: salvage or amputation. *J Bone Joint Surg [Am]* 1987;69-A:799-800.
20. **Lange RH.** Limb reconstruction versus amputation decision making in massive lower extremity trauma. *Clin Orthop* 1989;243:92-9.
21. **Bosse MJ, MacKenzie EJ, Kellam JF, et al.** A prospective evaluation of the clinical utility of the lower-extremity injury-severity scores. *J Bone Joint Surg [Am]* 2001;83-A:3-14.
22. **Bergner M, Bobbitt RA, Carter WB, Gilson BS.** The Sickness Impact Profile: development and final revision of a health status measure. *Med Care* 1981;19:787-805.
23. **David SM, Gruber HE, Meyer RA Jr, et al.** Lumbar spine fusion using recombinant human bone morphogenetic protein in the canine: a comparison of three dosages and two carriers. *Spine* 1999;24:1973-9.
24. **Fischgrund JS, James SB, Chabot MC, et al.** Augmentation of autograft using rhBMP-2 and different carrier media in the canine spinal fusion model. *J Spinal Disord* 1997;10:467-72.
25. **Groenveld HH, van den Bergh JP, Holzmann P, et al.** Histological observations of a bilateral maxillary sinus floor elevation 6 and 12 months after grafting with osteogenic protein-1 device. *J Clin Periodontol* 1999;26:841-6.
26. **Hecht BP, Fischgrund JS, Herkowitz HN, et al.** The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. *Spine* 1999;24:629-36.
27. **Hollinger JO, Schmitt JM, Buck DC, et al.** Recombinant human bone morphogenetic protein-2 and collagen for bone regeneration. *J Biomed Mater Res* 1998;43:356-64.
28. **Howell TH, Fiorellini J, Jones A, et al.** A feasibility study evaluating rhBMP-2/absorbable collagen sponge device for local alveolar ridge preservation or augmentation. *Int J Periodontics Restorative Dent* 1997;17:124-39.
29. **Hyder PR, Dowell P, Singh G, Dolby AE.** Freeze-dried, cross-linked bovine type I collagen: analysis of properties. *J Periodontol* 1992;63:182-6.
30. **Sugurdsson TJ, Nygaard L, Tatakis DN, et al.** Periodontal repair in dogs: evaluation of rhBMP-2 carriers. *Int J Periodontics Restorative Dent* 1996;16:524-37.
31. **Uludag H, Friess W, Williams D, et al.** rhBMP-collagen sponges as osteoinductive devices: effects of in vitro sponge characteristics and protein pI on in vitro rhBMP pharmacokinetics. *Ann NY Acad Sci* 1999;875:369-78.
32. **Govender S, Csimma C, Genant HK, et al.** Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. *J Bone Joint Surg [Am]* 2002;84-A:2123-34.
33. **Tarnuzzer RW, Schultz GS.** Biochemical analysis of acute and chronic wound environments. *Wound Repair Regen* 1996;4:321-5.
34. **Alberts KA, Loohagen G, Einarsdottir H.** Open tibia fracture: faster union after unreamed nailing than external fixation. *Injury* 1999;30:519-23.
35. **Bone LB, Kassmann S, Stegemann P, France J.** Prospective study of union rate of open tibial fractures treated with locked, unreamed intramedullary nails. *J Orthop Trauma* 1994;8:45-9.
36. **Singer RW, Kellam JF.** Open tibial diaphyseal fractures: results of undereamed locked intramedullary nailing. *Clin Orthop* 1995;315:114-18.
37. **Stegemann P, Lorio M, Soriano R, Bone L.** Management protocol for unreamed interlocking tibial nails for open tibia fractures. *J Orthop Trauma* 1995;9:117-20.
38. **Tornetta P 3rd, Bergman M, Watnik N, Berkowitz G, Steuer J.** Treatment of grade-III open tibial fractures: a prospective randomized comparison of external fixation and nonreamed locking nailing. *J Bone Joint Surg [Br]* 1994;76-B:13-19.
39. **Sheperd LE, Costigan WM, Gardocki RJ, et al.** Local or free muscle flaps and undreamed interlocked nails for open tibial fractures. *Clin Orthop* 1998;350:90-6.