Time to Union as a Measure of Effectiveness

Johan A.P.A.C. van Kollenburg, M.D., David Ring, M.D., Ph.D.

Orthopaedic Hand and Upper Extremity Service,, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Time to fracture union is commonly reported in orthopaedic clinical research even though there is no accepted reference standard for the radiological diagnosis of union, and radiographic diagnosis of union has not been shown to be reliable or precise. Studies have noted inconsistent definitions and measure of union both in orthopaedic scientific publications[1] as well as in a survey of orthopaedic traumatologists.[2] Several studies have also questioned the intra- and inter-observer reliability of radiographic diagnosis of union for various fractures.[3-7] The growing consensus that time to union is an unreliable and imprecise measure of the effectiveness of fracture treatment would be corroborated by identification of variance in the average time to union in studies of comparable fractures similarly treated.

In this study we catalogue the last 10 years' studies that use time to union as an outcome measure, recording diagnostic criteria and comparing mean time to union for comparable fractures with comparable treatment.

Methods

Pubmed was searched for English Language articles published during the 10-year period between 1997 and 2007 using the following terms: "time to union," time AND union, time AND bony AND healing, time AND fracture AND healing, time AND unite AND fracture, time AND bone AND unite. Exclusion criteria were (1) nonhuman studies, (2) studies of the treatment of ununited fractures, osteomyelitis, or peri-prosthetic fractures (3) case reports and (4) pediatric fractures.

The papers were evaluated in three ways. First, the following data were extracted: the method for diagnosing union; mean and range of "time to union"; the number of patients; fracture site and treatment; and the statistical methods used to evaluate time to union. Second, in order to evaluate variations in average "time to union" for comparable treatments of nearly identical fractures at identical anatomic sites, we selected sets of three or greater papers evaluating similar fracture treatment. Finally among all papers providing enough data to perform statistical comparisons, the average time to union was evaluated for statistically significant differences across studies using one-way analysis of variance. P values <0.05 were considered significant. For each statistically significant difference, post-hoc pair wise comparisons of the selected studies were performed using the Tukey test.

Results

One hundred twenty-seven studies met the inclusion criteria. Because of the number of studies and many anatomical areas, the areas were categorized by AO location. The following anatomical areas were involved: Ankle (3 studies); calcaneus (1); clavicle (3); distal femur (2); distal radius (1); tibial pilon (5); distal femur (21); floating knee (1); forearm (9); hip (13); humerus (10); long bones (2); mallet finger (1); metacarpal (1); metatarsal (1); proximal phalanx (1); scaphoid (6); segmental tibia (2); talus (1); tibial shaft (39), tibial plafond (4) and 1 trans-scaphoid perilunate fracture-dislocation.

Diagnosis of Fracture Union

There was variation in the diagnostic criteria for fracture union as follows: Bridging callus (39 studies), bridging callus at three different cortices (30), bridging callus in two different views (25), and bridging callus or obliteration of the fracture line (13), presence of callus (2), absence of osteonecrosis (1), absence of displacement (1), and hardware failure or loosening (1). The diagnostic criteria were not clearly stated in 27 studies.

Variation in Reported Time to Union for Specific Fractures

Most studies don't mention the interval time between follow-up appointments. Others have a monthly interval for follow-up, and some have a two-weekly follow-up. Ten specific fracture types had three or more studies addressing time to fracture union, comprising a total of 66 studies. The anatomical regions covered included: Upper extremity fractures: Clavicle (3); Forearm (3); Humerus (6) and Scaphoid (4); Lower extremity fractures: Distal Tibia (6); Femur (9); Hip (12); Tibia (8); Tibial plafond (3), and open tibia fractures. (12) There was substantial variance in mean time to union for all fractures.

Upper Extremity Fractures

The average mean time to union was 12.8 ± 2.6 weeks (range 9.6 – 16.4 weeks) among the three studies of clavicle fractures; 10.9 ± 2.7 weeks (range 7.8 – 16 weeks) among the six studies addressing humeral fractures treated with nailing or plating; 13.6 ± 5.2 weeks (range 6.4 – 20 weeks) among the three studies addressing forearm fractures; and 12.0 ± 5.0 weeks (range 6.1 – 18.2 weeks) among the four studies addressing operative management of scaphoid fractures.

Lower Extremity Fractures

The average mean time to union among seven studies addressing operative treatment of intertrochanteric femur fractures was 14.0 ± 3.1 weeks (range 10.2 – 19.5 weeks). The average mean time to union among three studies of the operative management of subtrochanteric femur fractures was 14.9 ± 0.7 weeks (range 14 – 15.7 weeks). The average mean time to union among nine studies of operative treatment of diaphyseal femur fractures was 18.2 ± 7.1 weeks (range 11.4 – 39.4 weeks).

The average mean time to union among three studies addressing tibial plafond fractures was 19.9 ± 2.6 weeks (range 16.5 – 22.8 weeks). The average mean time to union among eight studies addressing diaphyseal tibia fracture was 18.5 ± 3.6 weeks (range 13.6 – 25.7 weeks). The average time to union among 12 studies addressing surgical treatment of open diaphyseal tibia fractures was 32.1 ± 7.4 weeks (range 19 – 47.8 weeks). Among six studies addressing distal tibia fractures, the average time to union was 20.9 ± 5.8 weeks (range 14.7 – 35 weeks).

Statistical Comparison of Time to Union for Specific Fractures

Among studies that provided sufficient data to perform a statistical comparison, there were statistically significant differences in average time to union among two studies evaluating plate fixation of clavicle fractures[8,9] (mean 11.5 ± 1.8 weeks; p=0.03), three studies evaluating unreamed nailing of femur fractures (mean 25.9 ± 10.0 weeks, p <0.01; Post hoc Tukey--all significantly different from one another), and three studies evaluating reamed nailing of femur fractures (mean 19.3 ± 7.0 weeks, p <0.01; Post hoc Tukey--all significantly different from one another). There were no differences in four study groups evaluating plate and screw fixation of intertrochanteric femur fractures (mean 10.9 ± 0.6 weeks, P=0.29), three studies describing plating of distal tibia fractures (mean 20.0 ± 0.6 weeks; p=0.92), or three studies comparing intramedullary nailing of femur fractures (mean 17.1 ± 3.0 weeks; p=0.23).

Three studies compared unreamed nailing

techniques in closed tibia fractures. There was no significant difference between the studies of Larsen and colleagues[10], Uhlin and colleagues[11], and Karladani and colleagues[12] (mean 21.2 ± 3.2 weeks; p = 0.07). There was a significant difference between the four studies reporting time to union in tibia fractures treated with reamed nailing (mean 15.8 ± 1.5 weeks; p < 0.01). Post hoc Tukey HSD analysis found a significant difference between Emami and colleagues[13] and Tigani and colleagues[14]; Larsen and colleagues[10] and Tigani and colleagues[14]; and between Braten and colleagues[15] and Tigani and colleagues[14].

Discussion

This study and prior structured reviews[1,16] note that there is no reference standard for the radiographic diagnosis of fracture union. Furthermore, our analysis demonstrated substantial variation in reported time to union for comparable fracture types with comparable treatments and statistically significant differences between several comparable studies that provided adequate data for statistical comparison. Combined with analyses that question the precision and reliability of the diagnosis of fracture union[2,3], these findings bring into question the role of time to union as a useful and meaningful measurement of treatment effectiveness in studies of fracture treatment.

The observed variations in average time to union are likely the result of multiple factors, including, but not limited to: (1) variations in diagnostic criteria for union; (2) intra- and interobserver variation in the diagnosis of union; and (3) variations in the details of management. One must also consider differences in the number, spacing, and regularity of the office appointments to assess fracture healing as well as differences in the statistical technique for evaluating union.

Until there is a consensus technique for the diagnosis of fracture union that is reliable and precise, it is misleading to report measurements of time to union. Other measures of successful fracture healing, such as the absence of loosening or failure of implants a minimum one year after surgery, may prove more valid and reliable for the diagnosis of fracture union and are probably more applicable and relevant. The imprecision of time to union as a measure of treatment effectiveness makes it particularly susceptible to bias and therefore inadequate for scientific investigation.

References

1. Corrales LA, Morshed S, Bhandari M et al. Variability in the assessment of fracture-healing in orthopaedic trauma studies. J Bone Joint Surg Am. 2008;90(9):1862-1868.
2. Bhandari M, Guyatt GH, Swiontkowski MF et al. A lack of consensus in the assessment of fracture healing among orthopaedic surgeons. J Orthop Trauma. 2002;16(8):562-566.
3. 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 Br. 2002;84(1):15-18.
4. Anand A, Feldman DS, Patel RJ et al. Interobserver and intraobserver reliability of radiographic evidence of bone healing at osteotomy sites. J Pediatr Orthop B. 2006;15(4):271-272.
5. Blokhuis TJ, de Bruine JH, Bramer JA et al. The reliability of plain radiography in experimental fracture healing. Skeletal Radiol. 2001;30(3):151-156.
6. Davis BJ, Roberts PJ, Moorcroft CI et al. Reliability of radiographs in defining union of internally fixed fractures. Injury. 2004;35(6):557-561.
7. Dias JJ, Taylor M, Thompson J et al. Radiographic signs of union of scaphoid fractures. An analysis

of inter-observer agreement and reproducibility. J Bone Joint Surg Br. 1988;70(2):299-301.
8. Kabak S, Halici M, Tuncel M et al. Treatment of midclavicular nonunion: comparison of dynamic compression plating and low-contact dynamic compression plating techniques. J Shoulder Elbow Surg. 2004;13(4):396-403.
9. Coupe BD, Wimhurst JA, Indar R et al. A new approach for plate fixation of midshaft clavicular fractures. Injury. 2005;36(10):1166-1171.
10. Larsen LB, Madsen JE, Hoiness PR et al. Should insertion of intramedullary nails for tibial fractures be with or without reaming? A prospective, randomized study with 3.8 years' follow-up. J Orthop Trauma. 2004;18(3):144-149.
11. Uhlin B, Hammer R. Attempted unreamed nailing in tibial fractures: a prospective consecutive series of 55 patients. Acta Orthop Scand. 1998;69(3):301-305.
12. Karladani AH, Granhed H, Edshage B et al. Displaced tibial shaft fractures: a prospective randomized study of closed intramedullary nailing versus cast treatment in 53 patients. Acta Orthop Scand. 2000;71(2):160-167.
13. Emami A, Petren-Mallmin M, Larsson S. No effect of low-intensity ultrasound on healing time of intramedullary fixed tibial fractures. J Orthop Trauma. 1999;13(4):252-257.
14. Tigani D, Fravisini M, Stagni C et al. Interlocking nail for femoral shaft fractures: is dynamization always necessary? Int Orthop. 2005;29(2):101-104.
15. Braten M, Helland P, Grontvedt T et al. External fixation versus locked intramedullary nailing in tibial shaft fractures: a prospective, randomised study of 78 patients. Arch Orthop Trauma Surg. 2005;125(1):21-26.
16. Morshed S, Corrales L, Genant H et al. Outcome assessment in clinical trials of fracture-healing. J Bone Joint Surg Am. 2008;90 Suppl 1:62-67.

Appendix A: Papers Used for Analysis

1. Nonoperative treatment compared with plate fixation of displaced midshaft clavicular fractures. A multicenter, randomized clinical trial. J Bone Joint Surg Am. 2007;89(1):1-10.
2. Abalo A, Dossim A, Assiobo A et al. Intramedullary fixation using multiple Kirschner wires for forearm fractures: a developing country perspective. J Orthop Surg (Hong Kong). 2007;15(3):319-322.
3. Adams CI, Keating JF, Court-Brown CM. Cigarette smoking and open tibial fractures. Injury. 2001;32(1):61-65.
4. Adolfsson L, Lindau T, Arner M. Acutrak screw fixation versus cast immobilisation for undisplaced scaphoid waist fractures. J Hand Surg [Br]. 2001;26(3):192-195.
5. Ahrengart L, Tornkvist H, Fornander P et al. A randomized study of the compression hip screw and Gamma nail in 426 fractures. Clin Orthop Relat Res. 2002(401):209-222.
6. Alberts KA, Loohagen G, Einarsdottir H. Open tibial fractures: faster union after unreamed nailing than external fixation. Injury. 1999;30(8):519-523.
7. Ali F, Saleh M. Treatment of isolated complex distal femoral fractures by external fixation. Injury. 2000;31(3):139-146.
8. Antich-Adrover P, Marti-Garin D, Murias-Alvarez J et al. External fixation and secondary intramedullary nailing of open tibial fractures. A randomised, prospective trial. J Bone Joint Surg Br. 1997;79(3):433-437.
9. Arora R, Gschwentner M, Krappinger D et al. Fixation of nondisplaced scaphoid fractures: making treatment cost effective. Prospective controlled trial. Arch Orthop Trauma Surg. 2007;127(1):39-46.

10. Baixauli F, Sr., Baixauli EJ, Sanchez-Alepuz E et al. Interlocked intramedullary nailing for treatment of open femoral shaft fractures. Clin Orthop Relat Res. 1998(350):67-73.
11. Bar-On E, Sagiv S, Porat S. External fixation or flexible intramedullary nailing for femoral shaft fractures in children. A prospective, randomised study. J Bone Joint Surg Br. 1997;79(6):975-978.
12. Basumallick MN, Bandopadhyay A. Effect of dynamization in open interlocking nailing of femoral fractures. A prospective randomized comparative study of 50 cases with a 2-year follow-up. Acta Orthop Belg. 2002;68(1):42-48.
13. Bibbo C, Patel DV. The effect of demineralized bone matrix-calcium sulfate with vancomycin on calcaneal fracture healing and infection rates: a prospective study. Foot Ankle Int. 2006;27(7):487-493.
14. Bond CD, Shin AY, McBride MT et al. Percutaneous screw fixation or cast immobilization for nondisplaced scaphoid fractures. J Bone Joint Surg Am. 2001;83-A(4):483-488.
15. Braten M, Helland P, Grontvedt T et al. External fixation versus locked intramedullary nailing in tibial shaft fractures: a prospective, randomised study of 78 patients. Arch Orthop Trauma Surg. 2005;125(1):21-26.
16. Castillo RC, Bosse MJ, MacKenzie EJ et al. Impact of smoking on fracture healing and risk of complications in limb-threatening open tibia fractures. J Orthop Trauma. 2005;19(3):151-157.
17. Chapman JR, Henley MB, Agel J et al. Randomized prospective study of humeral shaft fracture fixation: intramedullary nails versus plates. J Orthop Trauma. 2000;14(3):162-166.
18. Chapman MW, Bucholz R, Cornell C. Treatment of acute fractures with a collagen-calcium phosphate graft material. A randomized clinical trial. J Bone Joint Surg Am. 1997;79(4):495-502.
19. Cheng MT, Chiu FY, Chuang TY et al. Treatment of complex subtrochanteric fracture with the long gamma AP locking nail: a prospective evaluation of 64 cases. J Trauma. 2005;58(2):304-311.
20. Chiu FY, Chen CM, Lin CF et al. Closed humeral shaft fractures: a prospective evaluation of surgical treatment. J Trauma. 1997;43(6):947-951.
21. Chong KW, Wong MK, Rikhraj IS et al. The use of computer navigation in performing minimally invasive surgery for intertrochanteric hip fractures--The experience in Singapore. Injury. 2006;37(8):755-762.
22. Clatworthy MG, Clark DI, Gray DH et al. Reamed versus unreamed femoral nails. A randomised, prospective trial. J Bone Joint Surg Br. 1998;80(3):485-489.
23. Clinkscales CM, Peterson HA. Isolated closed diaphyseal fractures of the femur in children: comparison of effectiveness and cost of several treatment methods. Orthopedics. 1997;20(12):1131-1136.
24. Collinge C, Kuper M, Larson K et al. Minimally invasive plating of high-energy metaphyseal distal tibia fractures. J Orthop Trauma. 2007;21(6):355-361.
25. Coupe BD, Wimhurst JA, Indar R et al. A new approach for plate fixation of midshaft clavicular fractures. Injury. 2005;36(10):1166-1171.
26. Court-Brown CM, Walker C, Garg A et al. Half-ring external fixation in the management of tibial plafond fractures. J Orthop Trauma. 1999;13(3):200-206.
27. Cox MA, Dolan M, Synnott K et al. Closed interlocking nailing of humeral shaft fractures with the Russell-Taylor nail. J Orthop Trauma. 2000;14(5):349-353.
28. Domb BG, Sponseller PD, Ain M et al. Comparison of dynamic versus static external fixation for pediatric femur fractures. J Pediatr Orthop. 2002;22(4):428-430.
29. Dujardin FH, Benez C, Polle G et al. Prospective randomized comparison between a dynamic hip screw and a mini-invasive static nail in fractures of the trochanteric area: preliminary results. J Orthop Trauma. 2001;15(6):401-406.
30. Egol KA, Dolan R, Koval KJ. Functional outcome of surgery for fractures of the ankle. A prospective, randomised comparison of management in a cast or a functional brace. J Bone Joint Surg Br. 2000;82(2):246-249.

31. Emami A, Petren-Mallmin M, Larsson S. No effect of low-intensity ultrasound on healing time of intramedullary fixed tibial fractures. J Orthop Trauma. 1999;13(4):252-257.
32. Finkemeier CG, Schmidt AH, Kyle RF et al. A prospective, randomized study of intramedullary nails inserted with and without reaming for the treatment of open and closed fractures of the tibial shaft. J Orthop Trauma. 2000;14(3):187-193.
33. Franck WM, Olivieri M, Jannasch O et al. Expandable nail system for osteoporotic humeral shaft fractures: preliminary results. J Trauma. 2003;54(6):1152-1158.
34. Friedlaender 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(Pt 2):S151-158.
35. Gao H, Luo CF, Zhang CQ et al. Internal fixation of diaphyseal fractures of the forearm by interlocking intramedullary nail: short-term results in eighteen patients. J Orthop Trauma. 2005;19(6):384-391.
36. Giannoudis PV, Hinsche AF, Cohen A et al. Segmental tibial fractures: an assessment of procedures in 27 cases. Injury. 2003;34(10):756-762.
37. Gill D, Hadlow A. The unreamed tibial rod in open tibial fractures. Aust N Z J Surg. 1997;67(12):869-871.
38. Gordon JE, Gregush RV, Schoenecker PL et al. Complications after titanium elastic nailing of pediatric tibial fractures. J Pediatr Orthop. 2007;27(4):442-446.
39. Gordon JE, Khanna N, Luhmann SJ et al. Intramedullary nailing of femoral fractures in children through the lateral aspect of the greater trochanter using a modified rigid humeral intramedullary nail: preliminary results of a new technique in 15 children. J Orthop Trauma. 2004;18(7):416-422; discussion 423-414.
40. 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(12):2123-2134.
41. Greenbaum B, Zionts LE, Ebramzadeh E. Open fractures of the forearm in children. J Orthop Trauma. 2001;15(2):111-118.
42. Hamilton RJ, Kelly IG. Evaluation of the long intra-medullary hip screw. Injury. 2004;35(12):1264-1269.
43. Harrington P, Nihal A, Singhania AK et al. Intramedullary hip screw versus sliding hip screw for unstable intertrochanteric femoral fractures in the elderly. Injury. 2002;33(1):23-28.
44. Harvey EJ, Agel J, Selznick HS et al. Deleterious effect of smoking on healing of open tibia-shaft fractures. Am J Orthop. 2002;31(9):518-521.
45. Henley MB, Chapman JR, Agel J et al. Treatment of type II, IIIA, and IIIB open fractures of the tibial shaft: a prospective comparison of unreamed interlocking intramedullary nails and half-pin external fixators. J Orthop Trauma. 1998;12(1):1-7.
46. Herrera A, Domingo LJ, Calvo A et al. A comparative study of trochanteric fractures treated with the Gamma nail or the proximal femoral nail. Int Orthop. 2002;26(6):365-369.
47. Herscovici D, Jr., Ricci WM, McAndrews P et al. Treatment of femoral shaft fracture using unreamed interlocked nails. J Orthop Trauma. 2000;14(1):10-14.
48. Hofmeister EP, Mazurek MT, Shin AY et al. Extension block pinning for large mallet fractures. J Hand Surg [Am]. 2003;28(3):453-459.
49. Horton TC, Hatton M, Davis TR. A prospective randomized controlled study of fixation of long oblique and spiral shaft fractures of the proximal phalanx: closed reduction and percutaneous Kirschner wiring versus open reduction and lag screw fixation. J Hand Surg [Br]. 2003;28(1):5-9.
50. Howe TS. Double level fractures of the femur treated with closed intramedullary nailing. Ann Acad Med Singapore. 1998;27(2):188-191.
51. Huckstadt T, Klitscher D, Weltzien A et al. Pediatric fractures of the carpal scaphoid: a retrospective clinical and radiological study. J Pediatr Orthop. 2007;27(4):447-450.

52. Inan M, Halici M, Ayan I et al. Treatment of type IIIA open fractures of tibial shaft with Ilizarov external fixator versus unreamed tibial nailing. Arch Orthop Trauma Surg. 2007;127(8):617-623.
53. Janssen KW, Biert J, van Kampen A. Treatment of distal tibial fractures: plate versus nail: a retrospective outcome analysis of matched pairs of patients. Int Orthop. 2007;31(5):709-714.
54. Jones BG, Duncan RD. Open tibial fractures in children under 13 years of age--10 years experience. Injury. 2003;34(10):776-780.
55. Kabak S, Halici M, Tuncel M et al. Treatment of midclavicular nonunion: comparison of dynamic compression plating and low-contact dynamic compression plating techniques. J Shoulder Elbow Surg. 2004;13(4):396-403.
56. Kai H, Yokoyama K, Shindo M et al. Problems of various fixation methods for open tibia fractures: experience in a Japanese level I trauma center. Am J Orthop. 1998;27(9):631-636.
57. Kakar S, Tornetta P, 3rd. Open fractures of the tibia treated by immediate intramedullary tibial nail insertion without reaming: a prospective study. J Orthop Trauma. 2007;21(3):153-157.
58. Kakar S, Tornetta P, 3rd. Segmental tibia fractures: a prospective evaluation. Clin Orthop Relat Res. 2007;460:196-201.
59. Kanabar P, Kumar V, Owen PJ et al. Less invasive stabilisation system plating for distal femoral fractures. J Orthop Surg (Hong Kong). 2007;15(3):299-302.
60. Karladani AH, Granhed H, Edshage B et al. Displaced tibial shaft fractures: a prospective randomized study of closed intramedullary nailing versus cast treatment in 53 patients. Acta Orthop Scand. 2000;71(2):160-167.
61. Keating JF, Blachut PA, O'Brien PJ et al. Reamed nailing of Gustilo grade-IIIB tibial fractures. J Bone Joint Surg Br. 2000;82(8):1113-1116.
62. Keating JF, O'Brien PJ, Blachut PA et al. Locking intramedullary nailing with and without reaming for open fractures of the tibial shaft. A prospective, randomized study. J Bone Joint Surg Am. 1997;79(3):334-341.
63. Kesemenli C, Subasi M, Necmioglu S et al. Treatment of multifragmentary fractures of the femur by indirect reduction (biological) and plate fixation. Injury. 2002;33(8):691-699.
64. Kesemenli CC, Kapukaya A, Subasi M et al. Early prophylactic autogenous bone grafting in type III open tibial fractures. Acta Orthop Belg. 2004;70(4):327-331.
65. Khan U, Smitham P, Pearse M et al. Management of severe open ankle injuries. Plast Reconstr Surg. 2007;119(2):578-589.
66. Kim SK, Oh JK. One or two lag screws for fixation of Danis-Weber type B fractures of the ankle. J Trauma. 1999;46(6):1039-1044.
67. Knoll VD, Allan C, Trumble TE. Transscaphoid perilunate fracture dislocations: results of screw fixation of the scaphoid and lunotriquetral repair with a dorsal approach. J Hand Surg [Am]. 2005;30(6):1145-1152.
68. Kubiak EN, Egol KA, Scher D et al. Operative treatment of tibial fractures in children: are elastic stable intramedullary nails an improvement over external fixation? J Bone Joint Surg Am. 2005;87(8):1761-1768.
69. Laohapoonrungsee A, Arpornchayanon O, Phornputkul C. Two-hole side-plate DHS in the treatment of intertrochanteric fracture: results and complications. Injury. 2005;36(11):1355-1360.
70. Larsen LB, Madsen JE, Hoiness PR et al. Should insertion of intramedullary nails for tibial fractures be with or without reaming? A prospective, randomized study with 3.8 years' follow-up. J Orthop Trauma. 2004;18(3):144-149.
71. Lee PC, Hsieh PH, Yu SW et al. Biologic plating versus intramedullary nailing for comminuted subtrochanteric fractures in young adults: a prospective, randomized study of 66 cases. J Trauma. 2007;63(6):1283-1291.
72. Lee VN, Srivastava A, Nithyananth M et al. Fracture neck of femur in haemophilia A - experience from a cohort of 11 patients from a tertiary centre in India. Haemophilia. 2007;13(4):391-394.
73. Leung F, Chow SP. A prospective, randomized trial comparing the limited contact dynamic compression plate with the point contact fixa-

tor for forearm fractures. J Bone Joint Surg Am. 2003;85-A(12):2343-2348.
74. Lim YJ, Lam KS, Lee EH. Open Gustilo 1 and 2 midshaft fractures of the radius and ulna in children: is there a role for cast immobilization after wound debridement? J Pediatr Orthop. 2007;27(5):540-546.
75. Lin J. Treatment of humeral shaft fractures with humeral locked nail and comparison with plate fixation. J Trauma. 1998;44(5):859-864.
76. Lin J, Hou SM. Antegrade locked nailing for humeral shaft fractures. Clin Orthop Relat Res. 1999(365):201-210.
77. Lin J, Hou SM. Unreamed locked tight-fitting nailing for acute tibial fractures. J Orthop Trauma. 2001;15(1):40-46.
78. Lin J, Hou SM, Hang YS. Locked nailing for displaced surgical neck fractures of the humerus. J Trauma. 1998;45(6):1051-1057.
79. Lindvall E, Haidukewych G, DiPasquale T et al. Open reduction and stable fixation of isolated, displaced talar neck and body fractures. J Bone Joint Surg Am. 2004;86-A(10):2229-2234.
80. Lindvall EM, Sagi HC. Selective screw placement in forearm compression plating: results of 75 consecutive fractures stabilized with 4 cortices of screw fixation on either side of the fracture. J Orthop Trauma. 2006;20(3):157-162; discussion 162-153.
81. Maneerit J, Meknavin S, Hanpanitkitkan S. Percutaneous versus open bone grafting in the treatment of tibial fractures: a randomized prospective trial. J Med Assoc Thai. 2004;87(9):1034-1040.
82. Maniscalco P, Gambera D, Bertone C et al. Healing of fresh tibial fractures with OP-1. A preliminary report. Acta Biomed. 2002;73(1-2):27-33.
83. Mikek M, Vidmar G, Tonin M et al. Fracture-related and implant-specific factors influencing treatment results of comminuted diaphyseal forearm fractures without bone grafting. Arch Orthop Trauma Surg. 2004;124(6):393-400.
84. Myers SH, Spiegel D, Flynn JM. External fixation of high-energy tibia fractures. J Pediatr Orthop. 2007;27(5):537-539.
85. Naique SB, 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(3):351-357.
86. Nork SE, Schwartz AK, Agel J et al. Intramedullary nailing of distal metaphyseal tibial fractures. J Bone Joint Surg Am. 2005;87(6):1213-1221.
87. Obremskey WT, Medina M. Comparison of intramedullary nailing of distal third tibial shaft fractures: before and after traumatologists. Orthopedics. 2004;27(11):1180-1184.
88. Oh CW, Park BC, Ihn JC et al. Primary unreamed intramedullary nailing for open fractures of the tibia. Int Orthop. 2001;24(6):338-341.
89. Ostrum RF. Treatment of floating knee injuries through a single percutaneous approach. Clin Orthop Relat Res. 2000(375):43-50.
90. Ostrum RF, Agarwal A, Lakatos R et al. Prospective comparison of retrograde and antegrade femoral intramedullary nailing. J Orthop Trauma. 2000;14(7):496-501.
91. Park SR, Kang JS, Kim HS et al. Treatment of intertrochanteric fracture with the Gamma AP locking nail or by a compression hip screw--a randomised prospective trial. Int Orthop. 1998;22(3):157-160.
92. Pehlivan O. Functional treatment of the distal third humeral shaft fractures. Arch Orthop Trauma Surg. 2002;122(7):390-395.
93. Pugh DM, Galpin RD, Carey TP. Intramedullary Steinmann pin fixation of forearm fractures in children. Long-term results. Clin Orthop Relat Res. 2000(376):39-48.
94. Qidwai SA. Intramedullary Kirschner wiring for tibia fractures in children. J Pediatr Orthop. 2001;21(3):294-297.
95. Raikin S, Froimson MI. Combined limited internal fixation with circular frame external fixation of intra-articular tibial fractures. Orthopedics. 1999;22(11):1019-1025.
96. Raschke M, Rasmussen MH, Govender S et al. Effects of growth hormone in patients with tibial fracture: a randomised, double-blind, pla-

cebo-controlled clinical trial. Eur J Endocrinol. 2007;156(3):341-351.
97. Rettig ME, Kozin SH, Cooney WP. Open reduction and internal fixation of acute displaced scaphoid waist fractures. J Hand Surg [Am]. 2001;26(2):271-276.
98. Ricci AR, Yue JJ, Taffet R et al. Less Invasive Stabilization System for treatment of distal femur fractures. Am J Orthop. 2004;33(5):250-255.
99. Ring D, Jupiter JB, Brennwald J et al. Prospective multicenter trial of a plate for dorsal fixation of distal radius fractures. J Hand Surg [Am]. 1997;22(5):777-784.
100. Ristiniemi J, Flinkkila T, Hyvonen P et al. RhBMP-7 accelerates the healing in distal tibial fractures treated by external fixation. J Bone Joint Surg Br. 2007;89(2):265-272.
101. Sadowski C, Lubbeke A, Saudan M et al. Treatment of reverse oblique and transverse intertrochanteric fractures with use of an intramedullary nail or a 95 degrees screw-plate: a prospective, randomized study. J Bone Joint Surg Am. 2002;84-A(3):372-381.
102. Scheerlinck T, Handelberg F. Functional outcome after intramedullary nailing of humeral shaft fractures: comparison between retrograde Marchetti-Vicenzi and unreamed AO antegrade nailing. J Trauma. 2002;52(1):60-71.
103. Seifert J, Stengel D, Matthes G et al. Retrograde fixation of distal femoral fractures: results using a new nail system. J Orthop Trauma. 2003;17(7):488-495.
104. Selvakumar K, Saw KY, Fathima M. Comparison study between reamed and unreamed nailing of closed femoral fractures. Med J Malaysia. 2001;56 Suppl D:24-28.
105. Shardlow DL, Giannoudis PV, Matthews SJ et al. Stabilisation of acute femoral fractures in Paget's disease. Int Orthop. 1999;23(5):283-285.
106. Sheerin DV, Turen CH, Nascone JW. Reconstruction of distal tibia fractures using a posterolateral approach and a blade plate. J Orthop Trauma. 2006;20(4):247-252.
107. Smith WR, Ziran B, Agudelo JF et al. Expandable intramedullary nailing for tibial and femoral fractures: a preliminary analysis of perioperative complications. J Orthop Trauma. 2006;20(5):310-314; discussion 315-316.
108. Stannard JP, Harris HW, McGwin G, Jr. et al. Intramedullary nailing of humeral shaft fractures with a locking flexible nail. J Bone Joint Surg Am. 2003;85-A(11):2103-2110.
109. Stannard JP, Wilson TC, Volgas DA et al. The less invasive stabilization system in the treatment of complex fractures of the tibial plateau: short-term results. J Orthop Trauma. 2004;18(8):552-558.
110. Subasi M, Kapukaya A, Arslan H et al. Outcome of open comminuted tibial plateau fractures treated using an external fixator. J Orthop Sci. 2007;12(4):347-353.
111. Swiontkowski MF, Aro HT, Donell S et al. Recombinant human bone morphogenetic protein-2 in open tibial fractures. A subgroup analysis of data combined from two prospective randomized studies. J Bone Joint Surg Am. 2006;88(6):1258-1265.
112. Syed AA, Agarwal M, Giannoudis PV et al. Distal femoral fractures: long-term outcome following stabilisation with the LISS. Injury. 2004;35(6):599-607.
113. Tigani D, Fravisini M, Stagni C et al. Interlocking nail for femoral shaft fractures: is dynamization always necessary? Int Orthop. 2005;29(2):101-104.
114. Tornetta P, 3rd, Tiburzi D. Antegrade or retrograde reamed femoral nailing. A prospective, randomised trial. J Bone Joint Surg Br. 2000;82(5):652-654.
115. Tornetta P, 3rd, Tiburzi D. Reamed versus nonreamed anterograde femoral nailing. J Orthop Trauma. 2000;14(1):15-19.
116. Tornetta P, 3rd, Tiburzi D. The treatment of femoral shaft fractures using intramedullary interlocked nails with and without intramedullary reaming: a preliminary report. J Orthop Trauma. 1997;11(2):89-92.
117. Trumble TE, Gilbert M, Murray LW et al. Displaced scaphoid fractures treated with open reduction and internal fixation with a cannulated

screw. J Bone Joint Surg Am. 2000;82(5):633-641.
118. Uhlin B, Hammer R. Attempted unreamed nailing in tibial fractures: a prospective consecutive series of 55 patients. Acta Orthop Scand. 1998;69(3):301-305.
119. Upadhyay A, Jain P, Mishra P et al. Delayed internal fixation of fractures of the neck of the femur in young adults. A prospective, randomised study comparing closed and open reduction. J Bone Joint Surg Br. 2004;86(7):1035-1040.
120. Vossinakis IC, Badras LS. The external fixator compared with the sliding hip screw for pertrochanteric fractures of the femur. J Bone Joint Surg Br. 2002;84(1):23-29.
121. Wang CJ, Liu HC, Fu TH. The effects of extracorporeal shockwave on acute high-energy long bone fractures of the lower extremity. Arch Orthop Trauma Surg. 2007;127(2):137-142.
122. Watson JT, Moed BR, Cramer KE et al. Comparison of the compression hip screw with the Medoff sliding plate for intertrochanteric fractures. Clin Orthop Relat Res. 1998(348):79-86.
123. Wei SY, Born CT, Abene A et al. Diaphyseal forearm fractures treated with and without bone graft. J Trauma. 1999;46(6):1045-1048.
124. Wiener BD, Linder JF, Giattini JF. Treatment of fractures of the fifth metatarsal: a prospective study. Foot Ankle Int. 1997;18(5):267-269.
125. Wong TC, Ip FK, Yeung SH. Comparison between percutaneous transverse fixation and intramedullary K-wires in treating closed fractures of the metacarpal neck of the little finger. J Hand Surg [Br]. 2006;31(1):61-65.
126. Wong TC, Yeung SH, Ip FK. The effectiveness of capsular decompression for internal fixation of intracapsular hip fractures. J Orthop Surg (Hong Kong). 2007;15(3):282-285.
127. Yoo MC, Cho YJ, Kim KI et al. Treatment of unstable peritrochanteric femoral fractures using a 95 degrees angled blade plate. J Orthop Trauma. 2005;19(10):687-692.