ORIGINAL ARTICLE



Comparative Outcome of Hybrid External Fixator Versus Primary Ilizarov Fixator in the Treatment of Open Distal Tibia Extra-Articular Fractures

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Received: 10 June 2022 / Accepted: 15 August 2022 / Published online: 8 September 2022 © Indian Orthopaedics Association 2022

Abstract

Introduction Because one-third of the tibia is subcutaneous throughout most of its length and its location, it is more prone to open fractures. Open distal tibia fractures are mostly due to RTA and sports injuries. The goal of treatment is to obtain a healed, well-aligned fracture; pain-free weight-bearing; and functional range of motion of the knee and ankle.

Materials and Methods 33 patients of the 18–60-year age group with open distal tibia extra-articular fractures (without vascular injury), less than 3 weeks old trauma were included in the prospective study for 1 year period (1st June 2019 to 31st May 2020). 17 cases were treated with the Hybrid external fixator (HEF) and 16 cases were treated with the Ilizarov fixator (IF). **Results** Significantly (P < 0.05), the mean duration of surgery was less in the HEF group (67.6 min), faster union of open type-II fractures in the HEF group (16.4 weeks), and also a higher AOFAS score at 6 months in open type-II fractures in the HEF group (84.4). There were two cases of equinus deformity in the IF group and one case of valgus deformity in the HEF group.

Conclusion HEF and IF are both equally effective in the treatment of open distal tibia extra-articular fractures with the advantage of stable fracture fixation, early weight-bearing, preserving soft tissue, minimal periosteal stripping, and providing one-staged definitive intervention. However, HEF is preferred over IF in terms of less operating time, faster union, and a better functional outcome with minimal complications.

Keywords Distal tibia fractures · Hybrid external fixator · Ilizarov fixator · AOFAS score

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Introduction

Distal tibia fractures are very common in day-to-day practise. Because of its location, the tibia is exposed to frequent injuries. It is the most commonly fractured long bone. Because one-third of the tibia is subcutaneous throughout most of its length, open fractures are more common in the tibia than in any other major long bone [1]. Distal tibia fractures include extra-articular fractures of the metaphysis and intra-articular pilon fractures. High-velocity trauma, including road traffic accidents and sports injuries, accounts for approximately 37.8% of all tibial injuries [2]. The challenges of treating these fractures are extremely damaged soft tissue as well as comminuted metaphyseal and articular comminution [3].

Treatment depends on the closeness to the tibial plafond, displacement of fracture, comminution, and injury to the soft tissue envelope [4]. There is a broad consensus that the status of the soft tissue is the first priority, because it is the basis of fracture healing [5]. The goal of the treatment is to achieve a healed, well-aligned fracture without the presence of infection; pain-free weight-bearing; and functional range of motion of the knee and ankle [6]

Surgical intervention for open fractures is commonly managed as one stage or multi-stage procedure with external and internal fixation [7]. Radical debridement of the wound outside the zone of injury, skeletal stabilization and early soft tissue coverage with a vascularized muscle flap is regarded as ideal management [8, 9]. Negative-pressure wound therapy (NPWT) is a potential method to manage soft tissue defects combined with high-grade open fractures, because it accelerates protein and collagen production, cell replication and reduces bacterial colonization of the wound [10]. The role of modern external fixators with circular frames and tension transfixion wires that do not span the ankle joint have gained popularity because these devices minimize soft tissue problems and allow for early joint motion while providing stability for fracture union [11]. Ilizarov and hybrid external fixator are two examples of such devices. Both methods have similar complications. Pin site infection is a major complication. In the case of circular ring fixators, pin site care and effective management of superficial infections are important to avoid deep infection [9]. There is a paucity of studies in the available literature to compare the outcome of Ilizarov fixator versus hybrid external fixator in the treatment of open distal tibia extra-articular fractures. We, therefore, want to study their efficacy in this regard for better treatment (Figs. 1,2).

Materials and Methods

In this study, we treated 17 cases of open distal tibia extra-articular fractures by hybrid fixator and 16 cases by Ilizarov fixator between 1st June 2019 and 31st May 2020. We included all distal tibia open fractures including extraarticular fractures, within 3 weeks duration of trauma and without vascular injuries. Institutional Ethics Committee clearance was obtained for the study. Patients having close fractures, old fractures (more than 3 weeks old), pathological fractures, and cases contraindicated for surgery were excluded from the study.

Initial Management of Open Fractures

The wound was exposed and bleeders, if any, were ligated. The wound was thoroughly washed with a copious amount of fluid. More than 9 L of fluid were used in type-III open fractures [13]. Contaminants and necrotic tissues were removed in the emergency room as much as possible. Stay sutures were applied in types II and III-A open fractures. The fractured limb was splinted with the help of a long leg POP slab. For type-I open fractures and clean type-II cases, third-generation cephalosporin was used. For contaminated type-II and all type-III fractures, one aminoglycoside and metronidazole were added [11]. All contaminated cases were debrided and operated as emergency cases within 24-48 h. Clean type-I and II cases were treated as elective cases. Involved side knee and ankle with tibia and fibula

Fig. 1 Cases treated with Hybrid external fixator (HEF)





After union



At 3 months



Follow-up at 6 months

Fig. 2 Cases treated with Ilizarov fixator (IF)



Immediate post-op



After union



At 3 months



Follow-up at 6 months

at full-length anteroposterior and lateral view. X-rays were taken of all patients, and a CT scan was done, if required.

Patients undergoing surgery were divided into two groups, group A and group B. Group A was treated with the Hybrid external fixator (HEF) and Group B was treated with an Ilizarov fixator (IF). The operation was done on a radiolucent table in the supine position.

Surgical Technique

After spinal anaesthesia, patients were put on a traction table without the application of a tourniquet. Pre-assembled rings (three full rings and four threaded rods between two rings) were sterilised before the procedure. Bony ends were curetted. All necrotic tissues and contaminants were removed. Wounds were washed with normal saline (NS). The ring assembly was introduced to the leg, then the first transverse wire was passed most distal to the fracture site near the ankle joint, parallel to the joint line. Another wire was inserted posterolateral to anteromedially proximal to the fracture just anterior to the fibular head. These two were reference wires. Both the tensioned wires were fastened to the proximal and distal rings. Reduction of the fracture site was achieved manually and with olive wire under intra-operative fluoroscopic guidance. All other wires were passed according to the safety corridor at least 45° to the first wire. Drop wires were also used to achieve a reduction. All the wires were fixed to the ring on one side and tensioned on other side according to fracture configuration. Only olive tip wires were not fixed to the ring before tensioning. After getting the reduction in all planes, rings proximal and distal to the fracture site were fastened with threaded rods. In all cases, 160 rings were used. For each ring, a minimum of two wires were used, out of which one wire was transtibiofibular [15, 16]. Muscles were at their maximum length while inserting the pins and all the wires were passed through safe zones. The wire sites were dressed with NS-soaked gauze. In the case of HEF, the distal full ring was applied as discussed above. The fracture was reduced under direct vision in large open fractures and under fluoroscopic guidance in the case of a small wound. Ankle spanning was not done as the reduction was stable. In case of extra-articular fractures, where adequate bone stock was available distally, a drop wire was used in the distal fragments to enhance the stability. After reduction, three 4.5 mm half pins were passed in the diaphysis. Half pins were passed through the normal soft tissue, pre-drilling was done. Half pins were introduced at variable angles. Half pins were then connected to a tubular connecting bar, and the same bar was fastened to the ring with a universal clamp or AO clamp. Another connecting bar was used to connect the previous bar and ring in an oblique fashion on the lateral side. Wounds that were amenable to closure were closed. Open wounds were later managed by plastic surgeons. The fibula was not fixed regularly as fibula fixation was not necessary in the case of external fixation [17]. Intravenous antibiotics were continued throughout the hospital stay. The post-operative dressing was done on the third day. After that regular dressing was done on the large and contaminated wounds. Pin track was cleaned with an NS swab daily and covered with betadine pellet for 1 week. After that, pin tracks were cleaned with NS swab twice daily. The rings and rods were cleaned with spirit daily. The post-operative equinus deformity was prevented by a sling fastened to the external fixator, which kept the limb in a plantigrade position. Static quadriceps, active knee bending, and ankle movements were started as early as possible depending on the pain threshold of the patients. Assisted weight-bearing was started early depending on fracture configuration. The patient was discharged between 7 and 14 days after the operation, depending on the soft tissue condition.

Follow-up

All patients were followed-up at an interval of 1 month, 3 months, and 6 months. At every visit, patients were assessed clinically regarding ankle range of motion, walking ability, fracture union, deformity, and shortening. American Orthopaedic Foot and Ankle Society (AOFAS) score [15] was used for evaluation. X-ray of the involved leg with ankle was done to assess fracture union and implant–bone interaction.

Cases were considered to have achieved union when there was no relative motion between fracture fragments and no tenderness at fracture sites clinically; union of any three cortices out of four in AP and lateral views radiologically. Delayed union was defined as when a fracture had not healed in the time frame that would be expected. Nonunion was defined as no union for up to 9 months or no radiological evidence of union for three consecutive months [17]. The cuts off for various deformity were varus $< 5^{0}$, valgus $< 5^{0}$, apex anterior/posterior $< 10^{0}$, rotation $< 0-10^{0}$, shortening < 10-12 mm. Functional assessment was done at 6 months. [19, 20]

Statistical Analysis

The statistical analysis of the data was performed using the computer program, Statistical Package for Social Sciences (SPSS for Windows, version 20.0.Chicago, SPSS Inc.) and Microsoft Excel 2010. Results on continuous measurements are presented as mean \pm standard deviations and are compared using a student t test. Discrete data were expressed as numbers (%) and were analysed using the Chi-square test and Fischer's exact test (where the cell counts were <5 or 0). The statistical significance was fixed at a 5% level (p value <0.05) for all analyses.

Results

Pre-operative Variables

Variables	Group A—HEF	Group B—IF $(n=16)$
	(n = 17)	
Mean Age	40.94 years	39.44 years
Sex	Male: 11 (64.7%); Female: 6 (35.3%)	Male: 12 (75%); Female: 4 (25%)
Mode of injury	RTA:11 (64.7%); self-fall:4 (23.6%); sports injury:2 (11.7%)	RTA:12 (75%); self- fall:3 (18.8%); sports injury:1 (6.2%)
Side of involvement	Right:10 (58.8%); Left:7 (41.2%)	Right:9 (56.2%); Left:7 (43.8%)
Gustilo and Ander- son [21, 22] clas- sification type of open fracture	Type I:6 (35.3%); Type II:5 (29.4%); Type III-A: 4 (23.5%); Type III- B:2 (11.8%)	Type I:5 (31.2%); Type II:4 (25%); Type III-A: 4 (25%); Type III-B:3 (18.8%)
Time interval between trauma and surgery	0–2 days: 13 (76.5%); 3–7 days: 4 (23.5%)	0–2 days: 13 (81.2%); 3–7 days: 3 (18.8%)
Mean duration of surgery	67.59 min	91.07 min
Mean duration of hospital stay	11.76 days	12.67 days

Union and Functional Outcome

Variables	Group A—HEF $(n=17)$	Group B—IF $(n=16)$
Mean AOFAS score [18] at 6 months	84.59 (open type-I:89.0; II:84.4; III:80.3)	84.27 (open type-I:89.6; II:81.5; III:81.71)
Mean time to union (in weeks)	16.47 (open type- I:14; II: 6.4; III:19.5)	16.81 (open type- I:14.2; II:17.75; III:18.3)
John and Wruh's criteria [20]	Excellent:8 (47.05%); Good:7 (41.2%); Fair:2 (11.8%)	Excellent:7 (43.8%); Good:8 (50%); Fair:1 (6.2%)

Complications

Complications	Group A—HEF $(n=17)$	Group B—IF $(n = 16)$
Deformity	Valgus malalignment 1 (5.9%)	Equinus 2 (12.5%)

Complications	Group A—HEF $(n = 17)$	Group B—IF $(n=16)$
Pint-tract infection	4 (23.5%)	4(25%)

Discussion

A comparative study was conducted to compare the efficacy of the Hybrid external fixator versus the Ilizarov fixator in the treatment of open distal tibia extra-articular fractures. In our study of 33 cases, 17 were treated with HEF, and 16 were treated with IF. The mean age in the study was 40.9 years in the HEF group and 39.4 in the IF group. The operating time was significantly less in the HEF group (67 min) compared to the IF group (91 min; P = 0.0008). There was no significant difference in mean AOFAS score at 6 months (P = 0.953), mean time to union (P=0.680), and duration of hospital stay (P=0.57) between two groups. Good–excellent functional outcome was seen in 88.25% of cases of HEF group and 93.8% of cases of IF group with a fair outcome of 11.75% of cases of HEF group and 6.2% of cases of IF group. The mean duration of hospital stay was 11.76 days in the HEF group and 12.67 days in the IF group. Union time was increased as the fracture severity increased. Open type-II fractures treated with HEF achieved union earlier than the IF group significantly (P=0.0385). Open type-II fractures treated with HEF had a higher AOFAS score at 6 months than the IF group significantly (P=0.0093). There were four cases of pin-tract infections each in both the groups; one case of valgus deformity in the HEF group, and two cases of equinus deformity in the IF group. Status of soft tissue, degree of comminution, and precarious blood supply make the plan of management difficult in distal tibial fractures. Long-term clinical outcome is affected by the mechanism of injury, the status of soft tissues, the degree of comminution, and articular damage. Open distal tibial fractures can be managed with conventional plating, minimally invasive plate osteosynthesis, uniplanar, biplanar, or circular external Fixators, and intramedullary interlocking nails. The conventional method of open reduction followed by plate and screw fixation provides good outcomes only in the fractures with less severe, lower energy trauma. Once complications including wound dehiscence and infection set in, patients will have a lengthy stay in the hospital. Often, they need multiple operations, and may even end up having an amputation. The role of modern external fixators with circular frames and tension transfixion wires that do not span the ankle joint has gained popularity, because these devices minimise soft tissue problems and allow for early joint motion while providing stability for fracture union. HEF provides stable fracture fixation; respects soft tissue, and allows an early range of motion and weight-bearing. It brings new complications like

pin-tract infection. It can be used as a primary or temporary device. [11, 25]

Comparison of HEF with Various Studies

Comparison of IF with Various Studies

Commle size	Maan fallow un	Deculto	Leung et al (2004)
26	36 months	Mean time to union at 4.2 months 81% Good–excel- lent outcome 3.85% varus mal- union 11.5% pin-tract infection	Demiralp et [28] (2007
48	14 months	 89.6% union rate Mean time to union at 3.6 months 10.4% non-union 14% superficial pin-tract infection 	Fadel et al [2 (2013)
162	52 months	98.15% union rate Mean time of union at 4.17 months 1.85% non-union 26% pin-tract infections	Our study
75	24 months	94% union rate 84% Good–excel- lent outcome 30% pin-tract infection	
17	12 months	100% union rate Mean time to union at 4.1 months 88.2% good–excel- lent & 11.8% fair outcome	
		5.8% valgus deformity 23.5% pin-tract infection	Conclus HEF and I period wi
	26 48 162 75	26 36 months 48 14 months 162 52 months 75 24 months	to union at 4.2 months 81% Good-excel- lent outcome 3.85% varus mal- union 11.5% pin-tract infection 48 14 months 89.6% union rate Mean time to union at 3.6 months 10.4% non-union 14% superficial pin-tract infec- tion 162 52 months 98.15% union rate Mean time of union at 4.17 months 1.85% non-union 26% pin-tract infections 75 24 months 94% union rate 84% Good-excel- lent outcome 30% pin-tract infection 17 12 months 100% union rate Mean time to union at 4.1 months 88.2% good-excel- lent & 11.8% fair outcome 5.8% valgus deformity 23.5% pin-tract

Studies	Sample size	Mean follow-up	Results
Leung et al [27] (2004)	30	28 months	96.7% Union rate Mean time to union at 13.9 weeks 70% good–excel- lent outcome 3.3% Non-union 29% pin-tract infections
Demiralp et al [28] (2007)	27	52 months	100% union rate Mean time to union at 14.1 months 18.5% pin-tract infections 11.1% loss of ankle joint motion
Fadel et al [29] (2013)	20	26 months	100% union rate Mean time of union at 18.6 weeks 100% good–exce lent outcome
Our study	16	12 months	100% union rate Mean time to union at 16.81 weeks 93.8% good- excellent outcome 25% pin-tract infections 12.5% equinus deformity

sion

IF both produce 100% union in a reasonable time period with the advantage of preserving soft tissue and minimal periosteal stripping. One of the advantages of both HEF and IEF is that, irrespective of soft tissue status, immediate and definitive operative intervention can be possible. Ankle joints can be spared by introducing multiple wires in a short distal fragment. It can be concluded that the HEF can produce a similar clinic-radiological outcome as IF with less operating time, less pin-tract infection, less technical demand, and less cost. However, the study may have limitations with respect to small sample size, quasi randomization and short follow-up. Due to short follow-up, not much can be commented on the post-traumatic arthritis and occupational rehabilitation of our patients.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard statement This article does not contain any studies with human or animal subjects performed by the any of the authors

Informed consent For this type of study, informed consent is not required.

References

- Rudloff JM. Fractures of the lower extremity. In: Azar FM, Beaty JH, Canale ST. editor. Campbell's Operative Orthopaedics.13th edition. Philadelphia PA; Elsevier;2017, 2740.
- Mahmood, A., & Kumar, G. (2014). Review of the treatment of distal tibia metaphyseal Fracture; plating versus intramedullary nailing: A systematic review of recent evidence. *Foot and ankle surgery*, 20(2), 151.
- Lerner, A., & Stein, H. (2004). Hybrid thin wire external fixation: An effective, minimally invasive, modular surgical tool for the stabilization of periarticular fractures. *Orthopaedics.*, 27, 59–62.
- Cheng W, Li Y, Manyi W. Comparison study of two surgical options for distal tibia fracture—minimally invasive plate osteosynthesis vs. open reduction and internal fixation. International orthopaedics. 2011 May 1;35(5):737–42.
- Wood GW 2. General principles of fracture treatment. In: Azar FM, Beaty JH, Canale ST. editor. Campbell's Operative Orthopaedics. Mosby 10th edition. Philadelphia PA; Elsevier;2003, 2671–2723.
- Rudloff MJ. Fractures of the lower extremity. In: Azar FM, Beaty JH, Canale ST. editor. Campbell's Operative Orthopaedics.13th edition. Philadelphia PA; Elsevier;2013, 2741.
- Huebner EJ, Ibiher N, Kubosch DC, Suedkamp NP, Strohm PC. Distal tibia fractures and pilon fractures. ActaChirOrthopTraumatolCech 2014; 167–176.
- Gopal, S., Majumder, S., Batchelor, A. G., Knight, S. L., De Boer, P., & Smith, R. M. (2000). Fix and flap: The radical orthopedic and plastic treatment of severe open fractures of the tibia. *Journal* of Bone and Joint Surgery. British Volume, 82, 959–966.
- Hutson, J., Dayicioglu, D., Oeltjen, J., Panthaki, Z., & Armstrong, M. (2010). The treatment of Gustilo grade IIIB tibia fractures with application of antibiotic spacer, flap, and sequential distraction osteogenesis. *Annals of Plastic Surgery*, 64, 541–552.

- Sibbald RG, Mahoney J, V.A.C.[®] Therapy Canadian Consensus Group. A consensus report on the use of vacuum-assisted closure in chronic, difficult-to-heal wounds. Ostomy Wound Manage 2003; 49: 52-66.
- Babies GC, Kontovazenitis P, Evangelopoulos DS, Tsailas p, Nikolopoulos K, Soucacos PN. Distal tibia fractures treated with hybrid external fixation. Injury 2010; 253–258.
- May, J. D., Paavana, T., McGregor-Riley, J., & Royston, S. (2017). Closed Tibial shaft fractures treated with the Ilizarov method: A ten years case series. *Injury*, 48(7), 1613–1615.
- S. Rajasekaran, A. Devendra, R. Perumal, J. Dheenadhayalan, and S.R. Sundararajan. "Initial Management of Open Fractures". in Rockwood and Green's fractures in Adults, 8th edition, Walter Kluwert, 2015; volume 1, chapter 10, p371–372.
- 14. British Orthopaedic Association recommendations (Open fractures of lower limb), Online Recommendations September 2009.
- Makhdoom, A., Maheshwari, L. D., Laghari, M. A., Tahir, S. M., Ali, S. M., & Siddiqui, K. A. (2015). Open proximal & distal fractures of tibia treated with Naseer Awais External Fixator with T-clamp. *The Journal of the Pakistan Medical Association*, 1(65), 727–732.
- Solomin L. The basic principles of external skeletal fixation using the Ilizarov device. Springer Science & Business Media; 2008 Sep 11.:184.
- Ristiniemi J,Flinkkila T,Hyvonem P,Lakovaara M,Pakarinen H,Biancari F,Jalovaara P.Two ring hybrid external fixation of distal tibial fractures:a review of 47 cases.J Trauma.2007 Jan;62(1):174–83.
- Kitaoka, H. B., Alexander, I. J., Adelaar, R. S., Nunley, J. A., Myerson, M. S., & Sanders, M. (1994). Clinical rating systems for the ankle-hindfoot, midfoot, hallux, and lesser toes. *Foot & ankle international.*, 15(7), 349–353.
- Weinlein JC.Delayed union and non-union of fractures. In: Azar FM, Beaty JH, Canale ST. editor. Campbell's Operative Orthopaedics, 13th edition. Philadelphia; Elsevier;2017; 3081–3082
- Boulton C and O'Toole RV. Tibia and Fibula Shaft Fractures. In: Charles MC, Heckman JD, McQueen MM, Ricci WM, Tornetta P. editor. Rockwood and Green's fractures in Adults, 8th edition, Philadelphia, Wolter Kluwer Health; 2015,2429.
- Gustilo, R. B., & Anderson, J. T. (1976). Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: Retrospective and prospective analyses. *Journal of Bone and Joint Surgery. American Volume*, 58, 453–538.
- Gustilo, R. B., Mendoza, R. M., & Williams, D. N. (1984). Problems in the management of type III (severe) open fractures: A new classification of type III open fractures. *Journal of Trauma*, 24, 742–746.
- Johner, R., & Wruhs, O. (1983). Classification of tibial shaft fractures and correlation with results after rigid internal fixation. *Clinical orthopaedics and related research.*, 1(178), 7–25.
- Leung, F., Kwok, H. Y., Pun, T. S., & Chow, S. P. (2004). Limited open reduction and Ilizarov external fixation in the treatment of distal tibial fractures. *Injury*, 35(3), 278–283.
- Tornetta 3rd P, Weiner L, Bergman M, et al. Pilon fractures: treatment with combined internal and external fixation. J Orthop Trauma 1993;7(6):489–96.
- Galante, V. N., Vicenti, G., Corina, G., Mori, C., Abate, A., Picca, G., Conserva, V., Speciale, D., Scialpi, L., Tartaglia, N., & Caiaffa, V. (2016). Hybrid external fixation in the treatment of tibial pilon fractures: A retrospective analysis of 162 fractures. *Injury*, 1(47), S131–S137.
- Scaglione, M., Celli, F., Casella, F., & Fabbri, L. (2019). Tibial pilon fractures treated with hybrid external fixator: Analysis of 75 cases. *Musculoskeletal surgery.*, 103(1), 83–89.
- Demiralp, B., Atesalp, A. S., Bozkurt, M., Bek, D., Tasatan, E., Ozturk, C., & Basbozkurt, M. (2007). Sprial and oblique fractures

of distal one-third of tibia-fibula: Treatment results with circular external fixator. *Annals-Academy Of Medicine Singapore.*, *36*(4), 267.

 Fadel, M., Ahmed, M. A., Al-Dars, A. M., Maabed, M. A., & Shawki, H. (2015). Ilizarov external fixation versus plate osteosynthesis in the management of extra-articular fractures of the distal tibia. *International orthopaedics.*, 39(3), 513–519. **Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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