Modern External Ring Fixation Versus Internal Fixation for Treatment of Severe Open Tibial Fractures

A Randomized Clinical Trial (FIXIT Study)

Major Extremity Trauma Research Consortium (METRC)*

Background: Modern external ring fixation has been hypothesized to reduce complications requiring hospital readmission compared with internal fixation when treating patients with high-energy open tibial shaft fractures. In this study, the 1-year probability of a major limb complication was compared between external and internal fixation of severe open tibial fractures.

Methods: This multicenter randomized clinical trial included patients 18 to 64 years of age with severe open tibial shaft fractures randomly assigned to either modern external ring fixation (n = 127) or internal fixation (n = 133). The primary outcome was a major limb complication within 365 days after randomization; these complications included amputation, infection, a soft-tissue problem, nonunion, malunion, and a loss of reduction/implant failure.

Results: Of 260 randomized patients, 254 were included in the final analysis. Their mean age (standard deviation) was 39 (13) years; 214 (84%) were men. The probability of at least 1 major limb complication was higher for external fixation (62.1% [95% confidence interval (CI): 53.4% to 70.8%]) than internal fixation (43.7% [95% CI: 35.5% to 52.9%]), with a risk difference of 18.4% (95% CI: 5.8% to 30.4%); p = 0.005). The most notable difference was in loss of reduction/implant failure, the rate of which was higher for external fixation (risk difference: 14.4% [95% CI: 7.0% to 21.6%]; p = 0.002). There was no appreciable difference in the probability of deep infection between external fixation (26.1%) and internal fixation (29.7%) (risk difference: −3.5% [95% CI: −14.8% to 7.8%]; p = 0.54). There were also no appreciable differences in the probabilities of amputation, nonunion, soft-tissue problems, malunion, or fracture healing between the groups.

Conclusions: These results argue against routine use of modern external ring fixation for the treatment of these severe open tibial fractures.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Open tibial shaft fractures are common injuries associated with poor outcomes and high rates of complications[1-12]. Traditional treatment protocols utilize intramedullary nails or plates for fracture fixation, which involve placing metal at the open fracture site. Studies indicate that infection rates increase when an implant is placed within a wound, likely due to the difficulty that the immune system has in clearing bacteria from biofilm that can develop on metallic surfaces[13-15]. Treatment with modern external ring fixation, which does not place any implant at the fracture site, is therefore thought to reduce rates of deep infection and potentially also reduce overall complication rates.

Although there is a theoretical basis to support an advantage of modern external ring fixation[4,6,16], it is unknown if this treatment performs better than the more commonly used internal fixation in terms of major complications. The aim of this randomized clinical trial was to examine the effect of modern external ring fixation compared with internal fixation on the probability of a major limb complication in patients with a severe open tibial shaft fracture.

Materials and Methods

Trial Design and Oversight

The trial was conducted at 20 U.S. trauma centers under the coordination of the Major Extremity Trauma Research Consortium[17,18]. It was registered in ClinicalTrials.gov (NCT01494519).

*A list of the METRC members is included in a note at the end of the article.

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJS/G993).

A **data-sharing statement** is provided with the online version of the article (http://links.lww.com/JBJS/G995).

Participants

Eligible patients were between 18 and 64 years of age at the time of randomization and had an open diaphyseal or metaphyseal tibial fracture. We included all Gustilo-Anderson Type-IIIB tibial fractures and a subset of severe Gustilo-Anderson Type-IIIA fractures that are considered to be at an elevated risk for complications[18,19]. Influenced by the Lower Extremity Assessment Project (LEAP), we defined the severe Type-IIIA subset according to the following criteria: (1) injuries with extensive contamination or muscle damage precluding safe internal fixation at the first debridement, (2) skin that could be closed after extensive muscle removal, (3) a bone gap of >1 cm after debridement, or (4) performance of fasciotomies for impending or diagnosed compartment syndrome with the wound not able to be closed primarily[20]. Type-IIIB fractures, by definition, required a soft-tissue flap if the limb was left at anatomic length and rotation. Detailed criteria are provided in Supplement 1 (see Appendix).

Randomization and Blinding

Within each site, we block-randomized patients in a 1:1 ratio to receive either modern external ring fixation or internal fixation. Randomization was performed with a central computerized system with variable block sizes that were not disclosed to the sites. There was no practical way to blind patients, surgeons, and research coordinators to the treatment assignment.

Interventions

The clinical course of the patients in both treatment groups followed standard protocols, including the use of temporary external fixation, the administration of antibiotics, weight-bearing protocols, and use of thromboembolic prophylaxis. Surgeons were instructed to avoid variations in treatment protocol based on treatment assignment.

Modern External Ring Fixation

Definitive treatment was with a U.S. Food and Drug Administration (FDA)-approved ring fixator, from any manufacturer, with at least 1 ring proximal and 1 ring distal to the fracture site. Surgeons applying external fixation in the study had to meet certain expertise criteria as detailed in the protocol in Supplement 1 (see Appendix).

Internal Fixation

Definitive treatment was with an FDA-approved locked intramedullary nail and/or plate. Since nails and plates are the most commonly used treatments, there was no training or expertise requirement for surgeons to perform this treatment.

Outcomes

All outcomes refer to the time period within 365 days after randomization. We defined the start time as the date of randomization. The time from randomization to definitive treatment was expected to be longer for external fixation compared with internal fixation as ring fixator placement is commonly delayed for some weeks to facilitate management of flaps and other soft-tissue issues. As a result, using the time of definitive treatment as the start time could have introduced bias as it might have led to the exclusion of more major limb complications between randomization and definitive treatment in the external fixation group than in the internal fixation group.

The primary outcome was the occurrence of any of 6 major limb complications requiring surgery or rehospitalization, including amputation, infection, a soft-tissue problem, nonunion, malunion, or a loss of reduction/implant failure. Infection was subclassified as deep infection, superficial infection, or pin-track infection. All deep infections were treated with surgical debridement, whereas superficial infections were treated with antibiotics only. Loss of reduction/implant failure was defined as a return to the operating room for an adjustment of the implant or reduction that was not related to the treatment of another complication such as infection or nonunion. While pin-track infections and implant adjustments are expected with external ring fixation, hospital readmission or operative treatment for these issues is nonetheless burdensome and costly for patients and was therefore included in our primary outcome. Bone defect treatment was at the discretion of the treating surgeon; however, planned bone grafts were not counted as a primary outcome. Definitions for each of these complications are detailed in Supplement 2 (see Appendix).

Secondary outcomes included (1) the number of major limb complications experienced by the patient, (2) occurrence of at least 1 major limb complication by type of complication, (3) the number of major limb complications of each type, (4) the number of operating room trips or same-day-surgery events for any reason, (5) the overall number of operations related to the study limb, (6) an operatively treated pin-track infection, (7) an operatively or nonoperatively treated pin-track infection, (8) the number of diagnosed pin-track infections, (9) the number of diagnosed major limb complications (of any type) that were nonoperatively treated, (10) the percentages of patients with the ring fixator still on the study limb at 365 days, and (11) fracture healing as determined prospectively by the treating surgeon.

Outcome Adjudication

All complications were independently adjudicated by 3 experienced orthopaedic trauma surgeons unaffiliated with the study as detailed in Supplement 2 (see Appendix). Due to the nature of the study interventions, it was not possible to blind the independent reviewers to treatment.

Statistical Analysis

Sample Size

The projected sample size was based on a 2-group comparison of the probability of at least 1 major limb complication within 365 days after randomization. It was assumed that this probability in the internal fixation arm would be 60% based on the overall complication rate observed in the LEAP study, in which 54% of the cohort consisted of severe tibial fractures[1]. Using a 2-sided alpha of 0.05 to test the null hypothesis of no treatment difference, it was determined that 140 patients per arm would provide 90% power to detect a 20% absolute reduction (35% relative reduction) in the probability of at least 1 major limb complication in the ring fixator arm. With 1 interim analysis planned using an O'Brien-Fleming boundary, the

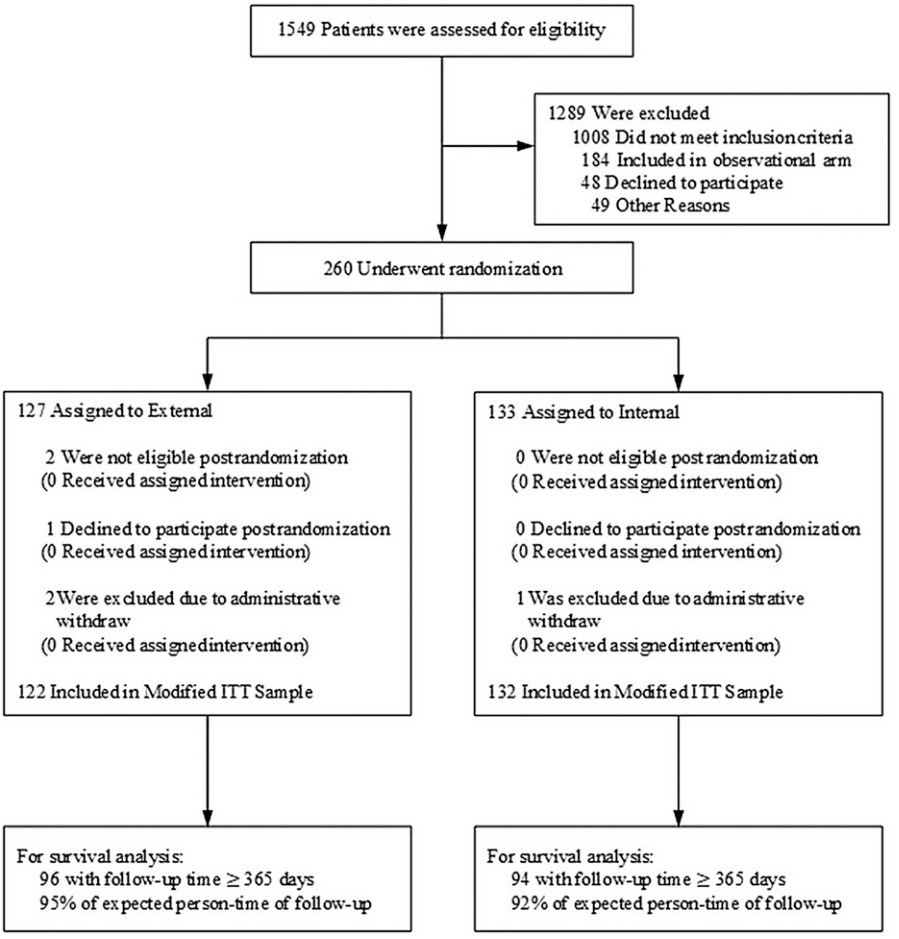

Fig. 1

Eligibility, randomization, and follow-up. ITT = intention to treat.

number of patients was inflated by 1% to preserve the overall type-I error rate. Accounting for 10% missing data, the proposed sample size was originally 156 per arm. Due to slower than expected enrollment, the power target was reduced to 80%, leading to a revised sample size of 121 per arm.

Interim Analysis

An interim analysis, reviewed by the Data and Safety Monitoring Board (DSMB) in April 2016, was conducted after half of the original sample size had a follow-up of at least 12 months. The DSMB recommended that the study was safe and ethical and it was appropriate to continue.

Analysis

Inferences about treatment effects were based on the intent-to-treat paradigm, in which patients were analyzed according to their assigned treatment group regardless of the treatment they received. Six patients were excluded after randomization: 2 patients had a Gustilo-Anderson Type-IIIC injury, confirmed by the treating surgeon, and were therefore ineligible; 1 patient withdrew immediately following randomization; and 3 patients were withdrawn in error by a study site.

Differences in the treatment-specific probability of events by 365 days were analyzed using Kaplan-Meier estimators. The treatment effects are reported as absolute risk differences and relative risks. Differences in the treatment-specific mean number of events by 365 days were analyzed, when possible, using zero-inflated Poisson and negative binomial regression models with a treatment indicator as the sole covariate and follow-up time as an offset (in the count part of the model). The treatment effects are reported as the incidence rate ratio (IRR). Since the 2 modeling approaches yielded similar results, only the zero-inflated Poisson results are presented. In a prespecified subgroup analysis, we compared study outcomes between patients with a severe Gustilo-Anderson Type-IIIA injury and those with a Type-IIIB injury. We performed interaction tests to evaluate subgroup differences. The detailed statistical analysis plan is provided in Supplement 3 (see Appendix). The data were analyzed using R version 3.6.3 (R Foundation for Statistical Computing) and Stata version 16.1 (StataCorp)[21,22].

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TABLE I Baseline Demographics and Injury Characteristics

	External Fixation (N = 122)	Internal Fixation (N = 132)
Mean age (std. dev.) *(yr)*	39.1 (13.3)	39.0 (12.7)
Male sex *(no. [%])*	107 (88)	107 (81)
Non-Hispanic White *(no. [%])*	55 (45)	63 (48)
College education *(no. [%])*	39 (32)	42 (32)
Working prior to injury *(no. [%])*	84 (69)	101 (77)
No health insurance *(no. [%])*	34 (28)	35 (27)
Mean body mass index (std. dev.) *(kg/m^2)*	27.9 (5.8)	28.5 (6.2)
Current tobacco use *(no. [%])*	56 (46)	57 (43)
Preinjury health excellent or very good *(no. [%])*	76 (62)	79 (60)
Gustilo-Anderson type *(no. [%])*		
"Severe" Type IIIA*	48 (39)	45 (34)
Type IIIB†	74 (61)	87 (66)
Tibial location (1 or more)‡ *(no. [%])*		
Proximal	8 (7)	17 (13)
Diaphyseal	110 (90)	107 (81)
Distal	17 (14)	24 (18)
Mean Injury Severity Score (std. dev.)§	14.1 (8.9)	14.9 (11.1)

*"Severe" Type IIIA was defined as (1) an injury that would have been classified as IIIB but because enough muscle was removed, the skin could be closed, (2) the bone gap was >1 cm after the debridement, or (3) fasciotomies were performed for impending or diagnosed compartment syndrome and wounds could not be closed primarily (i.e., needed skin graft). †For 5 patients with a Type-IIIB injury, the use of a flap was avoided by shortening and/or rotating the limb with a modern ring external fixator and then slowly restoring anatomy over time. This "soft tissue reduction" technique was anticipated to be a possibility and was allowed as part of the study protocol. ‡The tibial location was not known for 2 patients. §Excludes the study injury.

Results

Patient Characteristics

From July 2011 through September 2017, we randomly assigned 260 patients to modern external ring fixation (127 patients) or internal fixation (133 patients). The final 12-month follow-up assessments were completed in October 2018. Of the 260 patients who underwent randomization, 254 (98%) were included in the final analysis (122 in the external fixation group and 132 in the internal fixation group). Follow-up was 95% of the expected person-time through 365 days for the external fixation group and 92% for the internal fixation group (Fig. 1).

Most patients were male (n = 214, 84%), and the mean age was 39 years (range, 18 to 64 years). Most fractures were diaphyseal (n = 217, 85%), and 63% (n = 161) were Gustilo-Anderson Type IIIB (Table I and Appendix eTable 1).

Adherence to Assigned Intervention

Of the 122 patients analyzed in the external fixation group, 117 (96%) were definitively treated with a modern external ring fixator. Of the 132 patients analyzed in the internal fixation group, 124 (94%) were definitively treated with internal fixation (Table II). There were 2 unplanned crossovers in the external fixation group and 4 in the internal fixation group. Seven patients did not receive definitive treatment within 1 year; 5 of them underwent amputation before the definitive fixation procedure could be performed (Table II). Several patients in each group were switched to the other treatment after receiving definitive fixation to manage complications (Table II).

Primary Outcome

The probability of at least 1 major limb complication within 365 days was higher for external fixation (62.1% [95% confidence interval (CI)]: 53.4% to 70.8%) than internal fixation (43.7% [95% CI: 35.5% to 52.9%]), with an absolute risk difference of 18.4% (95% CI: 5.8% to 30.4%; p = 0.005) (Table III).

Secondary Outcomes

Of the 6 types of complication events, loss of reduction/implant failure showed the most notable difference between groups, with a higher risk in the external fixation group (risk difference: 14.4% [95% CI: 7.0% to 21.6%]; p = 0.002) (Table III). Patients were operatively treated to perform frame adjustments due to loss of alignment and/or problems with the frame, including soft-tissue impingement and mechanical loosening of the bone-implant interface due to failed wires or half pins. While the estimated difference in infection requiring surgery or hospital admission was also higher for external fixation, that difference was coupled with appreciable uncertainty (risk difference: 9.1% [95% CI: −2.9% to 20.9%]; p = 0.14) (Table III). There was no appreciable difference in the probability of deep

TABLE II Treatment Characteristics

	External Fixation (N = 122)	Internal Fixation (N = 132)
Definitive fixation		
Received assigned treatment *(no. [%])*	117 (96)	124 (94)
Unplanned treatment crossover* *(no. [%])*	2 (2)	4 (3)
Treatment switch after definitive fixation† *(no. [%])*	17 (14)	7 (5)
Did not receive definitive fixation‡ *(no. [%])*	3 (2)	4 (3)
Mean duration between randomization and definitive fixation (std. dev.) *(days)*	25.8 (35.1)	8.6 (36.5)
Plan to treat bone defect to promote healing§ *(no. [%])*	60 (49)	58 (44)
Mean no. of debridements for injury prior to or on day of definitive fixation	3.3	3.4
Temporary external fixation prior to definitive fixation *(no. [%])*	100 (82)	101 (77)
Nonoperative implant adjustments *(no. [%])*	53 (43)	19 (14)

*Two patients randomized to external fixation had definitive fixation with internal fixation, and 4 patients randomized to internal fixation had definitive fixation with a modern external ring fixator. †Definitive fixation according to treatment assignment but switched treatment (external to internal or internal to external) prior to 365 days. ‡Five patients underwent amputation and never received definitive fixation, 1 patient never transitioned from a temporary fixator, and 1 patient received definitive treatment with a nail 365 days after randomization due to prolonged concern about soft-tissue coverage and infection. §At the time of definitive treatment, surgeons were asked whether the treatment plan included treatment of a bone defect to promote healing. Treatments included but were not limited to bone grafting and distraction osteogenesis (ring fixation only).

infection for external fixation (26.1%) compared with internal fixation (29.7%) (risk difference: −3.5% [95% CI: −14.8% to 7.8%]; p = 0.54). There were more pin-track infections leading to hospital admission in the external fixation group (20.4% versus 0.8%; risk difference: 19.6% [95% CI: 12.0% to 27.0%]; p = 0.002) (Table III). For 8 of the 28 patients who had a pin-track infection, this infection was the only major limb complication event. Of these 8 patients, 3 were admitted to the hospital and treated with antibiotics and 5 underwent irrigation and debridement in the operating room to treat the infection. The average number of major limb complications was 1.66 (95% CI: 1.38 to 2.00) in the external fixation group versus 1.30 (95% CI: 1.02 to 1.66) in the internal fixation group (IRR: 1.28 [95% CI: 0.94 to 1.74]; p = 0.12) (see Appendix eTable 2).

The external fixation group had higher rates of operating room trips or same-day surgery (IRR: 1.22 [95% CI: 1.09 to 1.36]; p = 0.001), surgery related to the study injury (IRR: 1.23 [95% CI: 1.09 to 1.38]; p = 0.001), and diagnosed limb complications that were nonoperatively treated (IRR: 1.82 [95% CI: 1.02 to 3.24]; p = 0.04). They also had an increased probability of operatively and nonoperatively treated pin-track

TABLE III Comparison of Major Limb Complications Treated with Surgery or Hospital Admission within 365 Days After Randomization Between External and Internal Fixation Groups

	Kaplan-Meier Estimate (95% CI)		Treatment Effect (95% CI)		
	External Fixation (N = 122) *(%)*	Internal Fixation (N = 132) *(%)*	Risk Difference *(%)*	Relative Risk	P Value
Major limb complication	62.1 (53.4, 70.8)	43.7 (35.5, 52.9)	18.4 (5.8, 30.4)	1.42 (1.11, 1.81)	0.005
Amputation	4.9 (2.3, 10.7)	7.9 (4.3, 14.2)	−2.9 (−9.0, 3.2)	0.63 (0.23, 1.68)	0.35
Infection (any)	38.8 (30.7, 48.2)	29.7 (22.4, 38.6)	9.1 (−2.9, 20.9)	1.31 (0.92, 1.86)	0.14
Deep infection	26.1 (19.1, 35.0)	29.7 (22.4, 38.6)	−3.5 (−14.8, 7.8)	0.88 (0.59, 1.32)	0.54
Superficial infection leading to hospital admission	5.1 (2.3, 11.1)	0	—*	—*	—*
Pin-track infection leading to hospital admission	20.4 (14.2, 29.0)	0.8 (0.1, 5.7)	19.6 (12.0, 27.0)	24.74 (3.40, 179.98)	0.002
Soft-tissue problem	19.2 (13.2, 27.5)	18.9 (13.1, 26.9)	0.3 (−9.5, 10.1)	1.02 (0.61, 1.70)	0.95
Nonunion	24.2 (17.4, 33.1)	25.4 (18.4, 34.3)	−1.2 (−12.2, 9.9)	0.95 (0.61, 1.49)	0.83
Malunion	0.8 (0.1, 5.9)	0	—*	—*	—*
Loss of reduction or implant failure	16.9 (11.2, 24.9)	2.5 (0.8, 7.6)	14.4 (7.0, 21.6)	6.69 (2.04, 21.92)	0.002

*Statistical analysis not conducted due to sparse data.

infections (risk difference: 30.6% [95% CI: 21.6% to 39.1%]; $p < 0.001$) (see Appendix eTables 3 and 4). Patients in the external fixation group were more likely to have a ring fixator in place at 365 days compared with patients in the internal fixation group (35.6% versus 7.7%; risk difference: 27.9% [95% CI: 16.8% to 37.8%]; $p < 0.001$) (see Appendix eTable 5). For those who had a frame removed, the average time from definitive fixation to removal was 221 days (median, 209 days). There were no appreciable differences in the rates of amputation, nonunion, soft-tissue problems, malunion, or fracture healing between the internal and external fixation groups.

We found no evidence of different treatment effects for the study outcomes between severe Gustilo Type-IIIA and Gustilo Type-IIIB fractures (see Appendix eTables 6 through 10).

Discussion

Among patients with a severe open tibial shaft fracture, we found that definitive treatment with modern external ring fixators resulted in a higher probability of at least 1 major limb complication event compared with internal fixation, indicating no practical benefit of external ring fixation for this outcome. Prior retrospective studies indicated that ring fixators may have a lower deep infection rate[4,6,16]; however, we found no appreciable difference in deep infection rates between treatment groups. This result was surprising and is counter to the hypothesis that avoiding metal implant surfaces at the fracture site by using an external fixator would reduce infection risk.

The difference observed in the primary outcome was driven by the expected finding of an increased probability of surgery to adjust for implant malalignment in the external fixation group. Although pin-track infections that are typically treated on an outpatient basis with oral antibiotics are well known to occur with modern ring external fixation, a large proportion of patients (20%) were admitted to the hospital for treatment of pin-track infection. We found no appreciable differences in amputation, nonunion, or malunion rates or in the proportion of patients who had healing within 365 days, indicating that both treatments are reasonable alternatives when viewed through the lens of limb salvage with a well-aligned, healed fracture.

The results of this study also demonstrated that, in both treatment groups, the proportion of patients with major complications, including infection, exceeded 40%. The complication rates are similar to outcomes reported in the LEAP study 25 years ago, indicating that little progress has been made in reducing complications[1]. Many patients did not have a healed fracture at 1 year, indicating that these injuries still have long treatment courses and high complication rates regardless of treatment. The use of topical antibiotic powder and antibiotic-coated implants may hold promise for reducing infectious complications in the future[23].

To our knowledge, this is the first multicenter randomized clinical trial in the U.S. comparing modern external ring fixators to internal fixation for severe open tibial shaft fractures. Although there have been smaller randomized trials comparing external and internal fixation, those studies either did not examine modern external ring fixators or did not focus on severe open injuries[24-28]. The strengths of our trial include the multicenter randomized design with well-balanced treatment groups. The relatively large sample size and enrollment across 20 centers strengthen generalizability. The internal validity of our findings is strengthened by a central, independent adjudication of outcomes.

The trial had several limitations. First, although there is likely no difference in expertise in internal versus external fixation of fractures in general, there was probably less experience with modern external ring fixators than with internal fixation, which may have biased results in favor of internal fixation. To attempt to limit this effect, surgeons had to attend a training session on external ring fixation prior to the study, have sufficient experience with external ring fixation, or be at a center with an experienced surgeon willing to perform the external fixation procedures in study participants. Alternatively, we could have allowed only a small subset of sites with experts in the use of modern external ring fixators to participate; however, that would have made the study impractical and would have limited generalizability. The lack of blinding is also a limitation of our study. We attempted to minimize potential biases that this may have introduced by employing independent outcome adjudication.

Of note, there are differences between the secondary outcomes in our paper and those listed in ClinicalTrials.gov. The secondary outcomes in the paper were all prespecified prior to database lock and analysis and match those listed in our statistical analysis plan. These secondary outcomes were added to provide information to the reader regarding the individual components of our composite primary outcome, more details regarding infection outcomes, as well as sensitivity analyses on the definition of the primary outcome. The secondary outcomes listed in ClinicalTrials.gov that are not included in this paper (limb function, patient-reported outcomes, pain, satisfaction with treatment, and health-care cost) are all planned to be addressed in subsequent publications.

Another limitation of this study is that we excluded 6 patients from the analysis after randomization. While this may have theoretically introduced bias, we believe that it had no appreciable effect due to the small number of exclusions.

Conclusions

This multicenter randomized trial provides evidence that modern external ring fixation for the treatment of severe open tibial shaft fractures has a higher risk of major limb complications compared with internal fixation and does not reduce the rate of deep infections. These findings argue against its routine use in this setting.

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/G994). ■

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METRC consists of the METRC Writing Group Members and METRC Corporate Authors.

The METRC Writing Group Members include Robert V. O'Toole, MD, R Adams Cowley Shock Trauma Center, Baltimore, Maryland; Lisa Reider, PhD, METRC Coordinating Center at the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; Joshua L. Gary, MD, McGovern Medical School at The University of Texas Health Science Center at Houston, Houston, Texas (now at Keck School of Medicine of the University of Southern California, Los Angeles, California); Stephen M. Quinnan, MD, Ryder Trauma Center at the University of Miami, Miami, Florida (now at Paley Orthopedic & Spine Institute at St. Mary's Medical Center, West Palm Beach, Florida); James J. Hutson Jr., MD, Ryder Trauma Center at the University of Miami, Miami, Florida; Daniel O. Scharfstein, ScD, METRC Coordinating Center at the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (now at University of Utah School of Medicine, Salt Lake City, Utah); Yanjie Huang, ScM, METRC Coordinating Center at the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (now at University of Michigan, Ann Arbor, Michigan); Todd O. McKinley, MD, Indiana University Health Methodist Hospital, Indianapolis, Indiana; J. Spence Reid, MD, Penn State Health Milton S. Hershey Medical Center, Hershey, Pennsylvania; Renan C. Castillo, PhD, METRC Coordinating Center at the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; Michael J. Bosse, MD, Department of Orthopaedic Surgery, Carolinas Medical Center, Atrium Health Musculoskeletal Institute, Charlotte, North Carolina; and Ellen J. MacKenzie, PhD, METRC Coordinating Center at the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.

METRC Corporate Authors include *Brooke Army Medical Center:* Daniel J. Stinner, MD, PhD (now at Vanderbilt University Medical Center); Michael J. Beltran, MD (now at University of Cincinnati); Michelle M. Norton, MPH, MBA; *Carolinas Medical Center, Department of Orthopaedic Surgery, Atrium Health Musculoskeletal Institute:* Joseph R. Hsu, MD; Madhav A. Karunakar, MD; Rachel B. Seymour, PhD; Stephen H. Sims, MD; Caroline M. Barrett, MD (now at UNC Health); Christine Churchill, MA; Elizabeth C. Deans, MD (now at UNC Health); Kaitlyn Hurst, MD (now at Indiana University - Eskenazi Health); *Center for Orthopaedic Research and Education:* Debra L. Sietsema, PhD, MSN; *Denver Health and Hospital Authority:* David J. Hak, MD (now at Hughston Clinic Orthopedic Trauma); Cyril Mauffrey, MD, FACS; Corey Henderson Trujillo, MS (now at Rocky Vista University); *Florida Orthopaedic Institute:* Hassan Mir, MD, MBA; Anjan R. Shah, MD; Barbara Steverson, MHA; *Hennepin County Medical Center:* Andrew H. Schmidt, MD; Patrick Yoon, MD (now at Minneapolis Veterans Affairs Healthcare System); Jerald R. Westberg, BA; *Indiana University Health Methodist Hospital:* Greg E. Gaski, MD (now at Inova Fairfax Hospital); Lauren C. Hill, CCRC; *McGovern Medical School at The University of Texas Health Science Center at Houston:* Timothy S. Achor, MD; Mark R. Brinker, MD; Andrew M. Choo, MD; John W. Munz, MD; Mark L. Prasarn, MD; Stephen J. Warner, MD, PhD; Matthew C. Galpin, CCRC (now at REDCap Cloud); *MetroHealth Medical Center:* Heather A. Vallier, MD; John K. Sontich, MD (now at University Hospitals of Cleveland Medical Center, Case Western Reserve University); Mary Alice Breslin, BA; *Mission Hospital:* H. Michael Frisch, MD; Adam M. Kaufman, MD; Thomas M. Large, MD; C. Michael LeCroy, MD; *Orlando Regional Medical Center:* Joshua R, Langford, MD; *Penn State Health Milton S. Hershey Medical Center:* Andrea Horne, MA, CCRP; *R Adams Cowley Shock Trauma Center at the University of Maryland:* W. Andrew Eglseder, MD; Christopher T. LeBrun, MD; Jason W. Nascone, MD; Ray Pensy, MD; Marcus F. Sciadini, MD; Gerard Slobogean, MD; Yasmin Degani, MPH; Amanda Amundson, MPH, MSc (now at Seattle Children's Hospital); Nathan N. O'Hara, PhD, MHA; *Ryder Trauma Center at the University of Miami:* Gregory A. Zych, DO, FAOA; *Saint Louis University:* J. Tracy Watson, MD; *Stanford University Medical Center:* Michael J. Gardner, MD; *The University of California, San Francisco:* Theodore Miclau, MD; Saam Morshed, MD, PhD; Utku Kandemir, MD; Tigist Belaye, MPA; *University of Iowa:* J. Lawrence Marsh, MD; Catherine Fruehling, BA; *University of Mississippi Medical Center:* Patrick F. Bergin, MD; Matt L. Graves, MD; Clay A. Spitler, MD (now at University of Alabama at Birmingham); *University of Texas Southwestern Medical Center:* Medardo Maroto, MD (now at Spectrum Health); *University of Washington:* Conor P. Kleweno, MD; *University of Wisconsin:* Paul S. Whiting, MD; Christopher Doro, MD; David C. Goodspeed, MD; Gerald J. Lang, MD; Natasha M. Simske, BS; Alexander B. Siy, BS; *Vanderbilt University Medical Center:* William Obremskey, MD, MPH; Eduardo J. Burgos, MD (now at Fundación Santa Fe de Bogotá); Alex Jahangir, MD, MMHC; Manish Sethi, MD; Vamshi Gajari, MBBS; *Wake Forest Baptist Health:* Robert D. Teasdall, MD; Eben A. Carroll, MD; Jason J. Halvorson, MD; Anna N. Miller, MD (now at Washington University in St. Louis); James Brett Goodman, MBA; Martha B. Holden, AAS, AA; *Walter Reed National Military Medical Center:* Wade T. Gordon, MD (now at Guthrie Robert Packer Hospital); *METRC Coordinating Center at the Johns Hopkins Bloomberg School of Public Health:* Lauren E. Allen, MA; Jeromie M. Ballreich, PhD, MHS (now at Johns Hopkins Bloomberg School of Public Health); Anthony R. Carlini, MS; Gregory de Lissovoy, PhD, MPH (now at Johns Hopkins Bloomberg School of Public Health); Rachel Kirk, BS; Jason Luly, MS; Craig M. Remenapp, MS.

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