Article

Journal of Orthopaedic Surgery

Journal of Orthopaedic Surgery
25(2) 1–8

DOI: 10.1177/2309499017716242
journals.sagepub.com/home/osj
SAGE

Circular external fixation and cemented PMMA spacers for the treatment of complex tibial fractures and infected nonunions with segmental bone loss

Andries H van Niekerk[1], Franz F Birkholtz[1,2], Phillip de Lange[2], Kevin Tetsworth[3,4,5,6] and Erik Hohmann[2,6,7,8]

Abstract

Purpose: The purpose of this study was to compare the outcome of combined circular external fixation and cemented polymethylmethacrylate (PMMA) spacer application between a cohort of patients with grade 3 open fractures and infected tibial nonunions and concomitant segmental bone loss. **Methods:** The study was designed as a retrospective cohort study. All patients who were treated for complex tibial fractures or infected nonunions with segmental bone loss between 2009 and 2013 were included if they were aged between 16 years and 60 years, sustained acute traumatic grade 3 open tibial fractures, presented with infected nonunion, and were followed up for a minimum of 12 months. Patients with a history of ipsilateral tibial fractures, contralateral lower extremity fractures, polytrauma, chest, or abdominal trauma and patients with head injuries were excluded. Both groups were treated with aggressive debridement, circular external fixation, and antibiotic-impregnated PMMA spacer. Outcome measures were the time in the external fixator (EFT) and the external fixation index (EFI). **Results:** Twenty-four patients with a mean age of 32 ± 14.7 years were included. Twelve patients with a mean age of 32 + 14 years and a mean bone defect of 82 + 36 mm were treated for acute complex grade 3 open tibial fractures, and 12 patients with a mean age of 35.1 + 15.7 years and a mean bone defect of 50 + 26 mm were treated for infected nonunions. There was no significant difference ($p = 0.44$) between the groups for EFT (249 ± 99 days—tibial fractures; 255 ± 142 days—infected nonunion). There were significant between group differences ($p = 0.027$) for EFI (37.3 ± 9.1 cm/days—tibial fractures; 56 ± 14.5 cm/days—infected nonunion). **Conclusion:** The findings of this study suggest that patients were treated for infected nonunion with segmental bone loss using circular external fixation, distraction osteogenesis, and antibiotic-impregnated PMMA spacers, and the spacers may not offer any advantage over a conventional approach using the principles of osteogenesis only. In contrast, antibiotic-impregnated spacers for open tibial trauma were advantageous and reduced the EFI considerably.

Keywords

bone transport, distraction osteogenesis, external fixation, induced membrane, limb reconstruction, Masquelet technique, PMMA spacer

Level of Evidence: III.

---

[1] Department of Orthopaedic Surgery, University of Pretoria, Steve Biko Academic Hospital, Pretoria, South Africa
[2] Walk-a-Mile Centre for Advanced Orthopaedics, Netcare Unitas Hospital, Mediclinic Midstream Hospital, Pretoria, South Africa
[3] Department of Orthopaedic Surgery, Royal Brisbane Hospital, Brisbane, Australia
[4] Queensland University of Technology, Brisbane, Australia
[5] University of Queensland School of Medicine, Brisbane, Australia
[6] Orthopaedic Research Centre of Australia, Brisbane, Queensland, Australia
[7] Medical School, University of Queensland, Queensland, Australia
[8] School of Medicine, University of Pretoria, Pretoria, South Africa

Corresponding author:
Erik Hohmann, Medical School, University of Queensland, Queensland, PO Box 4045, Rockhampton QLD 4700, Australia.
Email: ehohmann@hotmail.com

Introduction

Tibial fractures are common injuries with an incidence between 8.1/100.000 and 37/100.00 per annum.[1] Of these fractures, approximately 25% are open injuries, and the majority of these are the result of high-energy trauma.[2,3] Surgical treatment is frequently required and includes appropriate soft-tissue management and early fracture stabilization.[3,4] Currently, the preferred options for fracture fixation are intramedullary nailing and external fixation.[3] Regardless of initial treatment, complication rates are high and include deep infection and nonunion. In a systematic review, Papakostidis et al. demonstrated that both infection and nonunion rates were significantly higher with fracture severity and increasing grading as per Gustilo–Anderson classification.[5] Significant bone loss due to high-energy trauma occurs in up to 11% of fractures.[6] Further debridement of devitalized bone often results in segmental defects and bone loss and is a more difficult problem to manage successfully.[5,6] In addition, the extensive debridement sometimes necessary for the treatment of deep infection can also contribute further to the associated bone loss.[7]

One of the currently accepted limb reconstruction techniques is distraction osteogenesis.[6–11] It is effective in promoting healing and eradicating long-standing osseous infections.[7] The induced membrane technique places a polymethylmethacrylate (PMMA) spacer for initial dead space management and if loaded with antibiotics can aid in the elimination of infection.[12] The formation of a biologic chamber provides vascularization, growth factors, prevents resorption of the regenerate, and acts as a conduit through which bone transport can occur without soft-tissue impingement.[12,13]

The purpose of this study was to compare the outcome of combined circular external fixation and cemented PMMA spacer application between a cohort of patients with grade 3 open fractures and infected tibial nonunions and concomitant segmental bone loss.

Methods

This study was conducted as a retrospective cohort study. All patients were identified from the departmental database who were treated for complex open tibial fractures or infected nonunions at a specialized limb reconstruction unit and trauma center between 2009 and 2013. Prior approval to conduct this review was obtained from the Institutional Review Board and Human Research Ethics Committee. Patients were included if they were aged between 16 years and 60 years, sustained acute traumatic grade 3 open tibial fractures or presented with an infected nonunion, and were followed up for a minimum of 12 months. The following exclusion criteria were applied: history of ipsilateral tibial fractures, contralateral lower extremity fractures, polytrauma, chest or abdominal trauma, and closed head injuries. Identified patients were divided into two groups, either acute grade 3 open tibial fractures or infected tibial nonunions.

Surgical treatment adhered to a standardized protocol. Initial debridement followed established principles, with resection of all necrotic and nonperfused tissue until healthy bleeding margins were observed.[14–16] Definition of involved nonviable tissue was determined by its clinical appearance, as judged by individual surgeons. Despite its subjective nature, this is consistent with prior publications and remains the best method available.[14–17] External fixation using a circular ring fixator was applied for fracture stabilization, and prophylactic or therapeutic fasciotomies were routinely performed when clinically indicated. An antibiotic-impregnated PMMA spacer (Palacos®; Zimmer, Warsaw, Indiana, USA) was inserted into the bone defect for local antibiotic delivery and to preserve space for definitive osseous reconstruction (Figures 1 and 2).[14,16] These spacers were shaped outside the body to limit thermal damage but were inserted prior to curing completely to allow modification of the spacer slightly to achieve overlap with the bone ends.[18,19] Soft-tissue coverage was performed within 48–72 h of presentation, with either an anterolateral thigh flap or latissimus free flap.

Following the primary procedure, patients were allowed to mobilize as tolerated. Tailored antibiotic therapy was commenced according to culture sensitivities and typically continued for 6 weeks. Routine serum levels of C-reactive protein (CRP) and white cell count (WCC) were checked every 2 weeks and the second stage was typically performed when the CRP and WCC returned to normal (CRP < 3 mg/L, WCC $< 10,000$ cells/ccm), and there was no clinical sign of infection (localized erythema, warmth, exudate, granulation tissue, and pyrexia). The second stage consisted of removal of the PMMA spacer, elevating the flap in a mini-open fashion opposite the vascular pedicle. The induced membrane was split longitudinally, preserved, and closed with resorbable sutures after the spacer was removed. A low-energy percutaneous corticotomy was performed as described by Paley and Tetsworth.[20] Distraction was commenced after a lag period of 7–10 days at a rate and rhythm of 1 mm daily in four increments of 0.25 mm. During bone transport, full weight bearing was encouraged. Once bone transport was completed, open docking was routinely performed. This consisted of debridement of both docking sites, opening of the medullary canal, and autologous bone grafting from the proximal tibia. Compression of the docking site was achieved through the circular ring fixator. Full weight bearing and functional loading as tolerated were encouraged following docking. Radiographic union was defined using Fishgrund's criteria,[21] with three of the four cortices continuous and at least 2 mm thick. The circular fixator was then destabilized for 7–10 days, and if there was no radiological evidence of deformity and patients were pain free, the fixator was removed thereafter. After fixator removal, the leg was protected in a functional boot for 6 weeks.

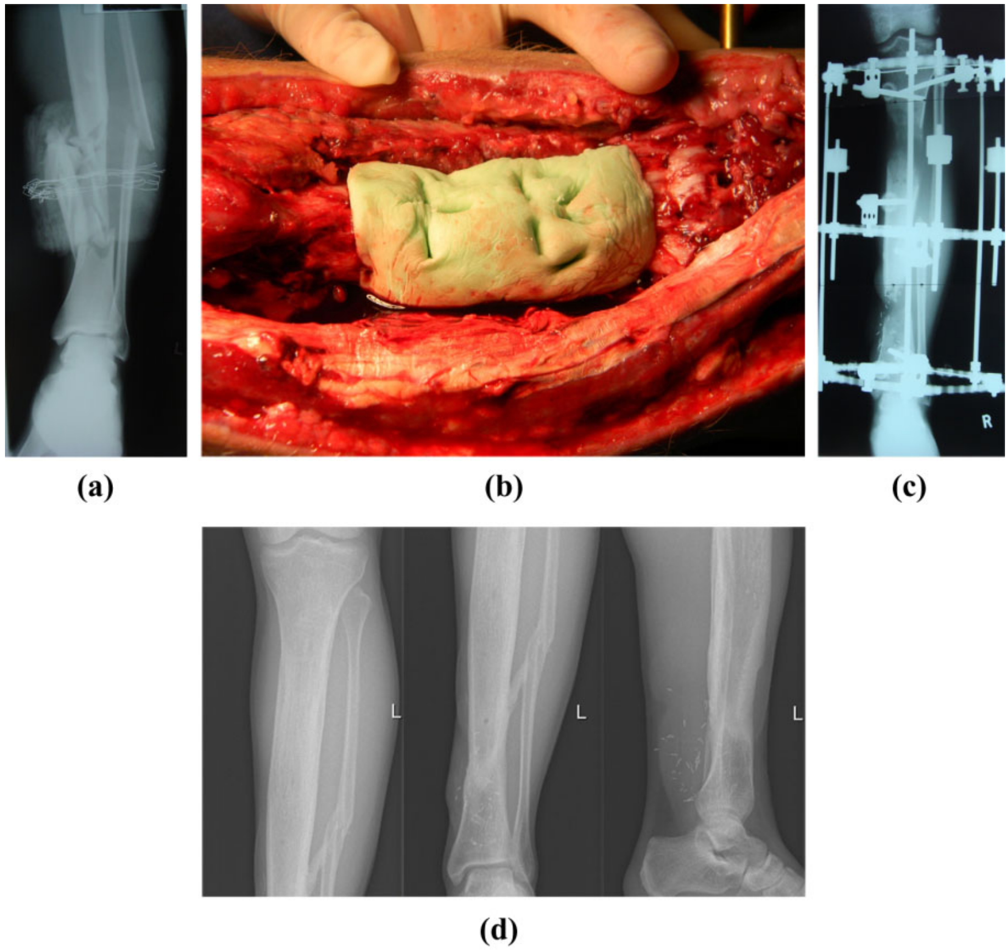

Figure 1. (a) A 29-year-old male sustained a grade 3B open tibial fracture during a motorcycle collision. (b) On debridement, a cement spacer was inserted into the 58 mm defect. (c) The cement spacer was removed at 6 weeks and bone transport performed. (d) Union was achieved after a total EFT of 284 days and an EFI of 49 days/cm. EFT: external fixator; EFI: external fixation index.

Outcome measures

The time in the external fixator (EFT) was recorded and defined as the time (days) from the initial application of the fixator until removal. The external fixation index (EFI) was calculated by dividing the time (days) in the EFT by the lengthening achieved (centimeters).

Statistical analysis

An a priori sample size calculation was performed, powered to detect a 50% difference between the trauma and infected nonunion cohorts using the following variables: medium effect size, $p = 0.05$, power of 0.8, $\mu = 38.1$ (derived from Fürmetz et al.,[22] standard deviation = 16.1, two tailed). Based on these parameters, the sample size calculations indicated that 11 patients per group were needed to provide 80% statistical power. In the event of significant findings, post hoc tests were performed using Tukey's test for pairwise comparisons. A Spearman rank test was used to investigate the strength of the relationship between EFT and distraction gap/bone defect size post debridement. Sample size calculations further indicated that a total of 19 patients were needed to establish correlations >0.6, with a significance level of $p = 0.05$ and power of 0.8 with a medium effect size. The critical r value that was needed to achieve significance for $df = 23$ and a two-tailed $p = 0.05$ was calculated to be 0.396. Descriptive statistics (means and standard deviation) were used for the demographic variables, and EFT and EFI. All analyses were conducted using STATA SE (version 12.0; StataCorp, College Station, Texas, USA) for Windows.

Results

Of the 26 patients initially identified, 24 patients with a mean age of 32 ± 14.7 years were included. One patient was less than 16 years old, and the standard protocol was not followed in one patient. Twelve patients were treated for acute complex trauma with grade 3 open tibial fractures. The mean bone defect in this group was 82 + 36 mm.

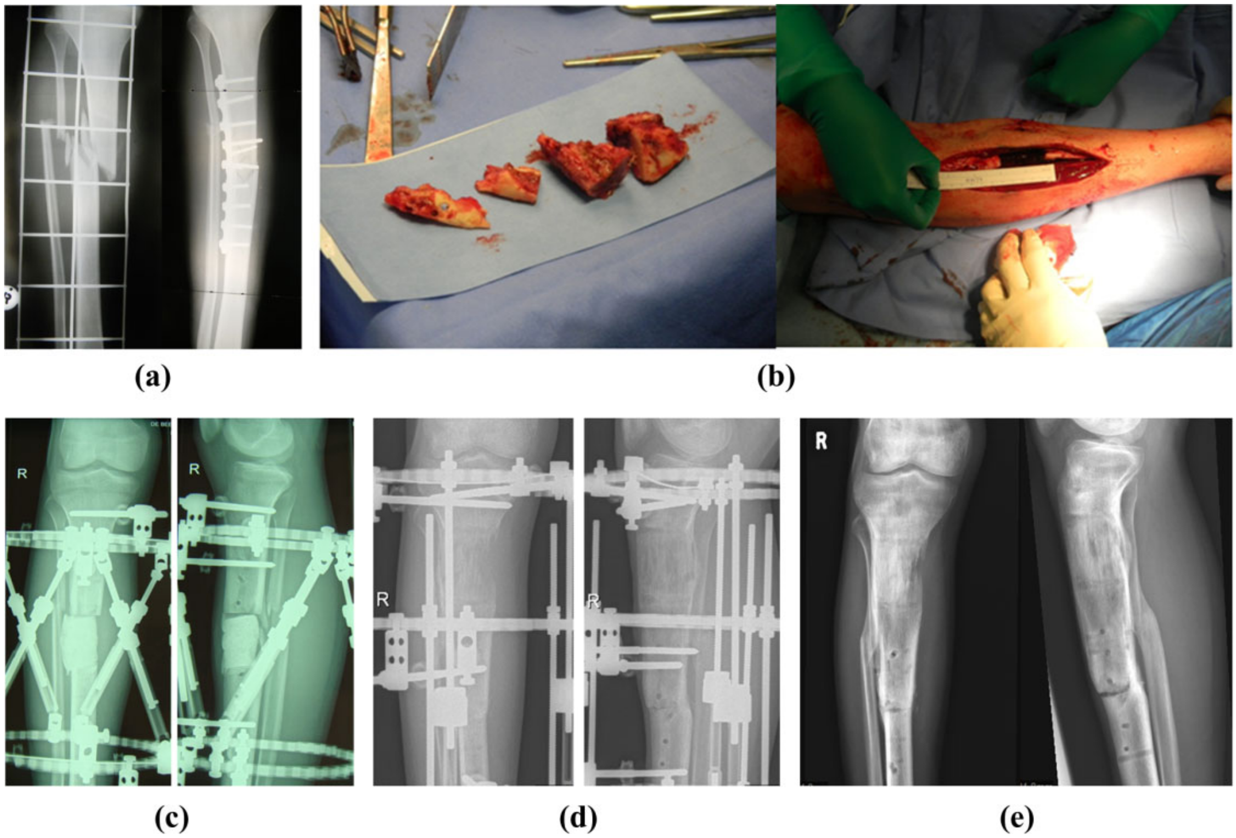

Figure 2. (a) A 21-year-old male developed a septic nonunion after sustaining a traumatic closed tibial fracture. (b) After debridement and removal of nonviable bone, a 45 mm bone defect was present. (c) An antibiotic-impregnated cement spacer was placed into the defect and removed after 7 weeks. (d) Distraction osteogenesis was performed after eradication of infection. (e) The total EFT was 231 days with an EFI of 51.3 days/cm. EFT: external fixator; EFI: external fixation index.

Twelve patients with a mean age of 35.1 + 15.7 year were treated for infected nonunions. The mean bone defect was 50 + 26 mm. The demographic details, mean bone defect size, and mean spacer times for both groups are summarized in Tables 1 and 2.

The mean external fixation time for both groups was 275 ± 121 days for the entire cohort. There was no significant difference ($p = 0.44$) between the group treated for tibial trauma (249 ± 99 days) and the group treated for infected nonunions (255 ± 142 days). The mean EFI for both groups was 46.9 ± 22.4 days/cm. There were significant differences ($p = 0.027$) between the group treated for tibial trauma (37.3 ± 9.1 cm/days) and the group treated for infected nonunions (56 ± 14.5 cm/days; Table 3). Spearman rank test revealed a highly significant ($p = 0.0001$) correlation ($r = 0.11$) between EFT and EFI. However, the relationship did not reach the critical r value.

Complications were observed in 50% of all patients. Pin tract infection occurred in seven patients and resolved with oral antibiotics and local pin tract care. In the infected nonunion group, one patient sustained a fracture through the regenerate which was treated with intramedullary nailing. Nonunion and persistent deep infection was observed in a 32-year-old immunocompromised human immunodeficiency virus (HIV)-positive male patient who had to undergo above-knee amputation as a salvage procedure. One patient sustained a stress fracture at the docking site and was treated conservatively. In the trauma cohort, one patient with a mangled extremity and attempted limb reconstruction had a persistent nonunion and opted for below-knee amputation. One patient required two adjustments of his circular fixator and leg lengthening for a 4 cm short tibia. The overall union rate was 91.7%.

Discussion

The most important finding of this study was that there was a significantly longer EFI for the group of patients treated for infected nonunion using circular external fixation, distraction osteogenesis, and antibiotic-impregnated PMMA spacer insertion compared to a cohort treated for grade 3 open tibial fractures with segmental bone loss. These differences are clinically even more significant when considering that the bone defect in the tibial fracture group was 64% larger and spacer time was 22% shorter. Following spacer removal, it took an average of 19 more days to grow

Table 1. Demographic details of all patients included and the subdivided groups.

	Patients (*n*)	Age years)	Gender	Grade III open fracture	Mechanism of injury
Total	24	33 ± 14.7	M = 16; F = 8	N = 23	MVA = 5; MBA = 3; fall = 3; direct trauma = 8; sports injury *n* = 1; PVA = 1; other trauma *n* = 3; gunshot injury *n* = 0
Sepsis	12	33.6 ± 4.4	M = 6; F = 6	N = 11	MVA = 4; MBA = 0; fall = 2; direct trauma = 3; sports injury *n* = 1; PVA = 0; other trauma *n* = 2; gunshot injury *n*=0
Trauma	12	32 ± 14	M = 10; F = 2	N = 12	MVA = 1; MBA = 3; fall = 1; direct trauma = 5; sports injury *n* = 0; PVA = 1; other trauma *n* = 1; gunshot injury *n* = 0

MVA: motor vehicle accident; MBA: motorbike accident; PVA: pedestrian vehicle accident.

1 cm of regenerate bone. Yin et al. demonstrated a mean EFI of 58 days in patients with infected nonunions treated with Ilizarov techniques and bone transport.[23] It appears that the induced membrane technique has no clinical advantages over a more conventional approach.

Anagnastakos et al. were able to demonstrate that antibiotic elution from antibiotic-impregnated PMMA spacers occurs and that localized concentrations can be 3–10 times higher than the minimal inhibitory concentrations (MICs) of the infecting organisms.[24] Using antibiotic PMMA spacers for the management of infected arthroplasty is a more common practice, with a variety of different options and established protocols.[25] The ideal duration of spacer implantation is currently unknown, and it has been suggested that the elution of antibiotics from the spacer only lasts for 10 days and less.[26] Van der Belt et al. investigated the release profiles of six different bone cements and were able to show that the released antibiotic fell below detection levels after 1 week.[27] Stevens et al. convincingly demonstrated the critical relationship between antibiotic elution and the mass of antibiotic added to the PMMA.[28] To achieve a prolonged release of antibiotic exceeding the MIC, it is essential to add very large quantities of powdered antibiotic. In this study, it is possible that the spacer was seeded with bacteria once the antibiotic concentration fell below the MIC. Ramage et al. reported bacterial concentrations of *Propionibacterium acnes* strains and the 10 most common Staphylococci strains.[29] The group was able to show that all bacteria built a biofilm and adhered to bone cement once elution rates fell below inhibitory concentrations.[29] Continued presence of low-grade infection within the induced membrane could explain the longer EFI in the infected nonunion group, resulting in slower bone formation but resolved with continued distraction osteogenesis. In contrast to cancellous bone grafting with the Masquelet technique, distraction osteogenesis in the presence of chronic infection may require a well-perfused healthy muscle and tissue envelope, something which the induced synovial pseudomembrane may not be able to provide.[18,30,31]

Another possible reason for the longer EFI in the infected nonunion group could be that the induced membrane is simply not required for bone transport in the presence of infection. Yin et al. pooled data from over 300 patients from 11 studies in a systematic review, and the EFI in their analysis was very similar to our results.[23] The results from this review constitute a very powerful argument that induced membranes in the presence of infection may not be necessary. Marais and Ferreira treated a small cohort of seven patients with distraction osteogenesis and cement spacer in a very similar environment, and their mean EFI was similar to our results with a mean of 79 days/cm.[12] However, three patients were active smokers which could explain the longer duration. Spiegl et al. reported an EFI of 59 days/cm in patients with chronic osteomyelitis which is comparable to both our results and

Table 2. Details of defect size and treatment for both groups.

	Flap cover	Mean time to reconstruction post-trauma (in days)	Defect size (in mm)	Mean spacer time (in weeks)
Total (*N* = 24)	Open # (*n* = 20)	N/A	66 ± 35	8.7 ± 3.2
Sepsis (*N* = 12)	Open # (*n* = 7)	N/A	50 ± 26	9.9 ± 3.6
Trauma (*N* = 12)	Open # (*n* = 12)	1.2 ± 1.2	82 ± 36	7.7 ± 2.2

N/A: not applicable.

Table 3. The results for EFT and EFI for both groups.

	EFT (days)	EFI (days/cm)
Total (*N* = 24)	275 + 121	46.9 + 22.4
Sepsis (*N* = 12)	255 ± 142	56.6 + 14.5
Trauma (*N* = 12)	294 ± 99	37.3 + 9.1
p Level	0.44	0.027

EFT: external fixator; EFI: external fixation index.

those of Yin, again confirming that induced membranes may not be needed.[32]

The mean EFI in the tibial fracture group was 37 days/cm for a mean bone defect of 82 mm. The bone defect in our small series is considerably larger than in other published series. Kristiansen et al. reported an EFI of 81 days/cm for a mean bone defect of 36 mm.[33] Wani et al. treated 60 patients with open tibial fractures with a mean bone defect of 48 mm and an EFI of 45 days.[34] Compared to these two studies, it appears that an antibiotic-impregnated spacer for open tibial trauma may be advantageous and reduces the EFI considerably. One of the possible reasons for the shorter EFI could be the demonstrated additional benefit of local antibiotic therapy in open tibial fractures.[35,36] Ostermann et al. demonstrated a significant reduction in the rate of deep infection in patients with grade III open fractures who received local antibiotic treatment to 3.7%, compared to 12% in patients who were only treated with systemic antibiotics.[36] The concept of an induced membrane in this scenario possibly provides a biological chamber, as described by Masquelet,[19] where prevention of infection is the primary objective, rather than eradication. In addition, the mean spacer time in the tibial fracture group was 23% shorter. In this situation, the prevention of fibrous tissue invasion and secretion of growth factors may stimulate bone formation and stabilize the regenerate. Pellisier et al. demonstrated higher concentrations of VEGF, TGF-β-1, and BMP-2 within the first 6 weeks in a rabbit model.[31] A later clinical study by Aho et al. showed that the highest expression of VEGF, IL-6, and Col-1 occurred at one month.[37] Therefore, the preferred timing for second stage procedures, whether cancellous bone grafting as described by Masquelet or bone transport, might be within 1 month of placing the PMMA spacer.[19] However, these are nonspecific growth factors and the value of their individual contributions toward fracture healing is uncertain. At this time, the optimal timing for PMMA spacer duration using an induced membrane reconstruction has not yet been definitively determined.

While we were able to demonstrate a highly significant ($p = 0.0001$) correlation ($r = 0.11$) between EFT and EFI, it did not reach the critical r value and was therefore clinically meaningless. We have performed an a priori sample size calculation and 19 patients were needed to achieve a power of 80% for $r > 0.6$; a post hoc test revealed that the study was underpowered (30%) for the given relationship. The relationships between the two variables are not well researched. Sakurakichi et al. suggested that the relationship between index and lengthening depends on age, etiology of shortening, and the amount bone shortening, with each case displaying its own curve.[38] Fishgrund et al. demonstrated that EFI is inaccurate except when the distraction gap is greater than 8 cm.[21] Both Sakurakichi and Fishgrund had rather small sample sizes, 28 and 114 patients, and even their findings may have been underpowered.[21,38] As a consequence, very large sample sizes may be needed to establish the true relationships between these two variables.

Complication rates were high and typically associated with the prolonged time in the circular fixator, distraction osteogenesis, infection, and bone and soft-tissue loss. Infection, especially pin tract infection is the most common sequelae with the application of external fixation and ranged from 0% to 50% in previous studies.[12,39,40] Our complication rates are comparable to these published studies and reflect the nature of the injury and the challenges associated with treatment. Seven patients (29%) experienced pin tract infection requiring systemic antibiotics. Two cases of nonunion were observed. Both patients were treated with amputation: in one case to salvage a persistent deep infection in a HIV-positive patient and in the other case the patient opted for below-knee amputation following high-energy trauma resulting in a mangled extremity. The overall nonunion rate was 8.3%.

This study has limitations. The retrospective design and its small sample size potentially introduces bias. However, an a priori sample size calculation was performed, and the study was adequately powered; in fact, a post hoc test revealed that the study had a power or 97% for EFI. As with all these complex disease patterns, the study cohort was heterogeneous, making it difficult to control possible confounding factors. Westgeet et al.[41] and O'Halloran et al.[42] showed that AO classification (odd ratio (OR) 1.86), gunshot wounds (GSW) (OR 1.98), fracture location and pattern (OR 0.46–1.36), open fractures (OR 3.9), smoking (OR 1.8), EtOH use (OR 1.6), HIV (OR 4), NSAID use (OR 1.5), diabetes (OR 2.2), compartment syndrome (OR 4), vascular injury (OR 2), muscle flap (9.6), and deep infection (OR 12.75) were variables that potentially influences union. However, it can be assumed that all factors with the exception of muscle flap soft-tissue cover (100% in the tibial fracture group, 58% in the infected nonunion group) and deep infection (0% in the tibial fracture group and 100% in the infected nonunion group) were equally distributed within the two groups and did not influence the results greatly. These two variables have certainly influenced the results as was intended with the study design and are not limitations per se. The follow-up of 12 months is rather short, and it cannot be completely excluded that more complications occurred later. However, the primary purpose of this study was to investigate EFI between the two groups; a variable that will not change with further follow-up. It cannot be entirely excluded that patients with grade 3 open fractures were not contaminated or had latent bone infections. However, the time to primary treatment including antibiotic-impregnated PMMA spacer placement was generally performed early, within 24 h. It can be safely assumed that in cases with deep latent infection, both the hematological and clinical signs would have later become evident. In addition, clinical signs of infection would likely have been observed during removal of the spacer.

Conclusion

The findings of this study suggest that patients were treated for infected nonunion with segmental bone loss using circular external fixation, distraction osteogenesis, and antibiotic-impregnated PMMA spacers, and the spacers may not offer any advantage over a conventional approach using the principles of osteogenesis only. In contrast, antibiotic-impregnated spacers for open tibial trauma were advantageous and reduced the EFI considerably.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Larsen P, Elsoe R, Hansen SH, et al. Incidence and epidemiology of tibial shaft fractures. *Injury* 2015; 46: 746–751.
2. Court-Brown CM and Caesar B. Epidemiology of adult fractures: a review. *Injury* 2006; 37: 691–697.
3. Hutchinson AJP, Frampton AE, and Bhattacharya R. Operative fixation for complex tibial fractures. *Ann R Coll Surg Engl* 2012; 94: 34–38.
4. Hildebrand F, van Griensven M, Huber-Lang M, et al. Is there an impact of concomitant injuries and timing of fixation of major fractures on fracture healing? A focused review of clinical and experimental evidence. *J Orthop Trauma* 2016; 30: 104–112.
5. Papakostidis C, Kanakaris NK, Pretel J, et al. Prevalence of complications of open tibial shaft fractures stratified as per Gustilo-Anderson classification. *Injury* 2011; 42: 1408–1415.
6. Keating JF, Simpson AHR, and Robinson CM. The management of fractures with bone loss. *J Bone Joint Surg Br* 2005; 87: 142–150.
7. Papakostidis C, Bhandara M, and Giannoudis PV. Distraction osteogenesis in the treatment of long bone defects of the lower limb. *Bone Joint J* 2013; 95B: 1673–1680.
8. Lavini F, Dall'Oca C, and Bartolozzi P. Bone transport and compression-distraction in the treatment of bone loss of the lower limbs. *Injury* 2010; 41: 1191–1195.
9. Paley D and Maar D. Ilizarov bone transport treatment for tibial defects. *J Orthop Trauma* 2000; 14(2): 76–85.
10. Song HR, Cho SH, Koo ST, et al. Tibial bone defects treated by internal bone transport using the Ilizarov method. *Int Orthop* 1998; 22: 293–297.
11. Tetsworth KD and Dlaska CE. The art of tibial bone transport using the Ilizarov fixator: the suspension wire technique. *Tech Orthop* 2015; 30: 142–155.
12. Marais LC and Ferreira N. Bone transport through an induced membrane in the management of tibial bone defects resulting from osteomyelitis. *Strategies Trauma Limb Reconstr* 2015; 10(1): 27–33.
13. Karger C, Kishi T, Schneider L, et al. Treatment of posttraumatic bone defects by the induced membrane technique. *Orthop Traumatol Surg Res* 2012; 98: 97–102.
14. Heitmann C, Patzakis MJ, Tetsworth KD, et al. Musculoskeletal sepsis: principles of treatment. *AAOS Instr Course Lect Ser* 2003; 52: 733–744.
15. Jordan DJ, Malahias M, Khan W, et al. The ortho-plastic approach to soft tissue management in trauma. *Open Orthop J* 2014; 31(8): 399–408.
16. Tetsworth K and Cierny GC. Osteomyelitis debridement techniques. *Clin Orthop Relat Res* 1999; 360: 87–96.
17. Bartlett CS, Helfet DL, Hausman MR, et al. Ballistics and gunshot wounds. Effects on musculoskeletal tissue. *J Am Acad Orthop Surg* 2000; 8: 21–36.
18. Masquelet A, Fitoussi F, and Begue T. Reconstruction des os longs par membrane induite et autogreffe spongieuse. *Ann Chir Plast Esthet* 2000; 45: 34653.
19. Masquelet AC and Begue T. The concept of induced membrane for reconstruction of long bone defects. *Orthop Clin N Am* 2010; 41: 27–37.
20. Paley D and Tetsworth K. Percutaneous osteotomies. Osteotomes and Gigli saw techniques. *Orthop Clin North Am* 1991; 22(4): 613–624.

21. Fishgrund J, Paley D, and Suter C. Variables affecting time to bone healing during limb lengthening. *Clin Orthop Relat Res* 1994; 301: 31–37.
22. Fürmetz J, Soo C, Behrendt W, et al. Bone transport for limb reconstruction following severe tibial fractures. *Orthop Rev (Pavia)* 2016; 8(1): 6384.
23. Yin P, Ji Q, Li T, et al. A systematic review and meta-analysis of Ilizarov methods in the treatment of infected non-union of tibia and femur. *Plos One* 2015; 10(11): e0141973.
24. Anagnostakos K, Fürst O, and Kelm J. Antibiotic-impregnated PMMA hip spacers. Current status. *Acta Orthop* 2006; 77(4): 628–637.
25. Tetsworth K. Infection after total knee arthroplasty: evaluation and treatment. *Curr Opin Orthop* 2003; 14: 45–51.
26. Elson RA, Jephcott AE and McGechie DB. Antiobiotic acryclic cement. *J Bone Joint Surg* 1977; 59B(2): 200–205.
27. Van de Belt H, Neut D, Uges DR, et al. Biomaterial-associated infection of gentamycin-loaded PMMA beads in orthopaedic revision surgery. *Biomaterials* 2000; 21: 1981–1987.
28. Stevens CM, Tetsworth KD, Calhoun JH, et al. An articulated antibiotic spacer for the management of infected total knee replacement: comparison of elution properties from simplex and palacos PMMA. *J Orthop Res* 2005; 23: 27–33.
29. Ramage G, Tunney MM, Patrick S, et al. Formation of Propionibacterium acnes biofilms on orthopaedic biomaterials and their susceptibility to antimicrobials. *Biomaterials* 2003; 24: 3221–3227.
30. Cattaneo R, Catagni M, and Johnson EE. The treatment of infected nonunions and segmental defects of the tibia by the methods of Ilizarov. *Clin Orthop Relat Res* 1992; 280: 143–152.
31. Pelissier P, Masquelet AC, Bareille R, et al. Induced membranes secrete growth factors including vascular and osteoconductive factors and could stimulate bone regeneration. *J Orthop Res* 2004; 22(1): 73–79.
32. Spiegl U, Pätzold R, Friederichs J, et al. Clinical course, complication rates and outcome of segmental resection and distraction osteogenesis after chronic tibial osteitis. *Injury* 2009; 44: 1049–1056.
33. Kristiansen LP, Steen H, and Reikeras O. No difference in tibial lengthening index by use of Taylor spatial frame or Ilizarov external fixator. *Acta Orthop* 2006; 77(5): 772–777.
34. Wani N, Baba A, Kangoo K, et al. Role of early Ilizarov ring fixator in the definitive management of type II, IIIa and IIIb open tibial shaft fractures. *Int Orthop* 2011; 35: 915–923.
35. Fuchs T, Stange R, Schmidmaier G, et al. The use of gentamycin-coated nails in the tibia: preliminary results of a prospective study. *Arch Orthop Trauma Surg* 2011; 131: 1419–1425.
36. Ostermann PA, Seligson D, and Henry SL. Local antibiotic therapy for severe open fractures. A review of 1085 consecutive cases. *J Bone Joint Surg Br* 1995; 77: 93–97.
37. Aho OM, Lehenkari P, Ristiniemi J, et al. The mechanism of action of induced membranes in bone repair. *J Bone Joint Surg Am* 2013; 95(7): 597–604.
38. Sakurakichi K, Tsuchiya H, Uehara K, et al. The relationship between distraction length and treatment indices during distraction osteogenesis. *J Orthop Sci* 2002; 7: 298–303
39. Ferreira N and Marais LC. Pin tract sepsis: incidence with the use of circular fixators in a limb reconstruction unit. *SA Orthop J* 2012; 11(1): 10–18.
40. Menakaya CU, Rigby AS, Hadland Y, et al. Fracture healing following high energy tibial trauma: Ilizarov versus Taylor Spatial Frame. *Ann R Coll Surg Eng* 2014; 96: 106–110
41. Westgeest J, Weber D, Dulai SK, et al. Factors associated with development of non-union or delayed healing after an open long bone fracture: a prospective cohort study of 736 subjects. *J Orthop Trauma* 2016; 30(3): 149–155.
42. O'Halloran K, Coale M, Costales T, et al. Will my tibial fracture heal? Predicting non-union at the time of definitive fixation based on commonly available variables. *Clin Orthop Relat Res* 2016; 474: 1385–1395.