RESEARCH PAPER

Local Antibiotic Delivery as an Adjunct to Systemic Prophylaxis for Prevention of Fracture-Related Infection in High-Energy Open Tibial Fractures

Dr. Tapankumar R. Patel[1], Dr. Parth Pavasiya[2], Dr. Mihir Tejura[3]*, Dr. Chetan Kothari[4], Dr. Himalaya Thumar[5]

[1]*Senior Resident, Department of Orthopaedics, BHRC, Pune, Maharashtra, India.*
[2]*Senior Resident, Department of Orthopaedics, BHRC, Pune, Maharashtra, India.*
[3]*Senior Resident, Department of Orthopaedics, GMERS Medical College and Civil Hospital, Morbi, Gujarat, India.*
[4]*Senior Resident, Department of Orthopaedics, BHRC, Pune, Maharashtra, India.*
[5]*Consultant Orthopedic Surgeon, Kashiba Multispeciality Hospital, Rajula, Amreli, Gujarat, India.*

Corresponding Author
* Dr. Mihir Tejura
Senior Resident, Department of Orthopaedics
GMERS Medical College and Civil Hospital
Morbi, Gujarat, India
Email: mihirt97ortho@gmail.com

Abstract

Background: High-energy open tibial fractures carry one of the highest rates of fracture-related infection (FRI) in orthopaedic trauma. Systemic antibiotic prophylaxis combined with early debridement is standard, yet infection remains a major cause of morbidity. Local antibiotic delivery may augment protection by producing bactericidal tissue concentrations without systemic toxicity.

Methods: One hundred and twenty adults with Gustilo–Anderson type II, IIIA, or IIIB open tibial diaphyseal fractures were randomised to systemic prophylaxis alone (Group A, n = 60) or systemic prophylaxis plus local antibiotics (Group B, n = 60) delivered as vancomycin powder in the wound and gentamicin-impregnated calcium sulfate beads. All patients underwent standardised debridement, temporary or definitive fixation, and 12 months of clinical and radiological follow-up. The primary outcome was FRI diagnosed by the 2018 international consensus definition.

Results: FRI occurred in 15/60 (25.0%) patients in Group A and 6/60 (10.0%) in Group B (p = 0.031; absolute risk reduction 15%, number needed to treat 7). The largest benefit was seen in Gustilo type IIIB injuries (43.8% vs 18.8%). Union rates and time to union favoured the local antibiotic arm without reaching significance. No systemic vancomycin toxicity was observed.

Conclusion: The addition of local antibiotic delivery to standard systemic prophylaxis significantly reduced FRI in high-energy open tibial fractures, with the greatest absolute benefit in the most severe injuries and no attributable systemic adverse events.

Keywords: *open tibial fracture; fracture-related infection; local antibiotics; vancomycin powder; calcium sulfate; Gustilo–Anderson.*

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.Introduction

The tibia is the most frequently fractured long bone, and because its anteromedial surface is covered by only a thin envelope of skin and subcutaneous tissue, it is also the most common site of open long-bone injury [1,2]. Open tibial fractures resulting from high-energy mechanisms carry an infection risk that far exceeds that of any other extremity fracture, with reported rates of deep infection ranging from 10% to more than 50% in the most severe Gustilo–Anderson subtypes [3,4]. Infection after open fracture prolongs hospitalisation, delays or prevents bone union, and is a leading indication for late amputation [5,6].

Modern management of open tibial fractures rests on the pillars of urgent intravenous antibiotic administration, thorough surgical debridement, skeletal stabilisation, and early definitive soft-tissue coverage [7,8]. Systemic antibiotic prophylaxis, first shown to be beneficial in the landmark trial of Patzakis and colleagues, is now supported by multiple guidelines and is universally accepted as the standard of care [9,10]. Nevertheless, systemically delivered antibiotics achieve only modest concentrations within traumatised, poorly perfused bone and haematoma, where bacterial contamination is most concentrated [11,12].

The concept of supplementing systemic prophylaxis with a locally delivered antibiotic depot addresses this pharmacokinetic gap. Local carriers release antibiotic directly at the fracture site at concentrations several orders of magnitude above the minimum inhibitory concentration, while maintaining serum levels well below the toxicity threshold [13,14]. Polymethylmethacrylate

(PMMA) beads impregnated with aminoglycosides have been used for more than three decades in the treatment of established osteomyelitis and, more recently, as prophylaxis in open fractures [15,16]. Bioabsorbable carriers such as calcium sulfate and calcium phosphate obviate the need for a second procedure to remove the depot and simultaneously provide osteoconductive scaffolding [17,18].

Intrawound vancomycin powder has attracted particular interest following its widespread adoption in spinal surgery, where several large series have documented reductions in surgical-site infection [19,20]. Application of vancomycin powder to open extremity fractures is intuitively attractive because it targets the Gram-positive organisms — particularly Staphylococcus aureus and methicillin-resistant S. aureus (MRSA) — that account for the majority of FRIs [21,22]. The recently completed VANCO pilot trial and the ongoing PREVENT CLOT and OXTIB studies have provided encouraging preliminary data, but a well-defined role for routine intrawound antibiotic prophylaxis in open tibial fractures has not yet been established [23,24].

The 2018 international consensus definition of fracture-related infection has, for the first time, provided reproducible diagnostic criteria that allow rigorous outcome comparison across studies [25]. Against this background we designed the present prospective randomised comparative study to assess whether the addition of local antibiotic delivery — combining intrawound vancomycin powder and gentamicin-impregnated calcium sulfate beads — to standard systemic prophylaxis reduces the incidence of FRI in adults with high-energy open tibial fractures.

Materials and Methods

Study design and setting

This prospective, single-centre, parallel-group randomised comparative study was conducted at a level-I trauma referral centre between January 2023 and December 2024. Institutional ethics committee approval was obtained (Ref. IEC/2022/OT-118) and the trial was registered prospectively with the national clinical trials registry. Written informed consent was obtained from every participant or their legally acceptable representative. The study was performed in accordance with the Declaration of Helsinki and reported using the CONSORT 2010 checklist [26].

Participants

Consecutive adults aged 18–65 years presenting within 12 hours of injury with a Gustilo–Anderson type II, IIIA, or IIIB open diaphyseal tibial fracture caused by a high-energy mechanism (road traffic collision, fall from height, or crush injury) were screened for eligibility [3]. Exclusion criteria were type I or type IIIC injuries, pathological or periarticular fractures, established infection at presentation, known hypersensitivity to vancomycin or gentamicin, pregnancy, immunocompromise (chronic corticosteroid use, HIV, active malignancy), an estimated glomerular filtration rate below 45 mL/min/1.73 m², and inability to complete 12 months of follow-up.

Randomisation and blinding

After confirmation of eligibility in the operating room following initial debridement, patients were randomised 1:1 to Group A (systemic antibiotics alone) or Group B (systemic antibiotics plus local antibiotic delivery) using computer-generated variable block randomisation stratified by Gustilo grade. Allocation was concealed in opaque sequentially numbered envelopes opened by the circulating nurse after the debridement stage was complete. Given the nature of the intervention, the operating surgeon could not be blinded; the outcome assessor performing follow-up infection adjudication and the microbiologist reporting cultures were blinded to allocation.

Interventions

All patients received intravenous cefuroxime 1.5 g every 8 hours from arrival, with the addition of gentamicin 5 mg/kg once daily for type III injuries, continued for 72 hours in accordance with contemporary BOAST and EAST guidelines [7,10]. Emergency management followed a standardised protocol: sterile saline-soaked dressing on arrival, tetanus prophylaxis, radiographs, and surgical debridement within a target of 6 hours of injury. Debridement consisted of extension of the traumatic wound, excision of devitalised tissue, delivery and inspection of bone ends, and pulsatile lavage with 9 L of normal saline. Skeletal stabilisation was achieved with a monolateral external fixator or reamed intramedullary nail depending on the injury pattern and soft-tissue status.

In Group B, immediately after debridement and before closure or dressing, 1 g of pharmaceutical-grade vancomycin powder was sprinkled over the fracture site and surrounding soft tissues, and 5–10 mL of gentamicin-impregnated calcium sulfate paste (containing 40 mg gentamicin per 10 mL) was moulded into beads and placed directly at the fracture surface and along the medullary canal when accessible. The dose of vancomycin was based on prior spinal and extremity literature [19,21]. Soft-tissue coverage — primary closure, delayed primary closure, split-thickness skin grafting, or local/free flap — was performed within 72 hours whenever possible in cooperation with the plastic surgery service, in line with the *fix-and-flap* principle described by Gopal and colleagues [27].

Outcome measures

The primary outcome was the diagnosis of FRI at any point during 12 months of follow-up, defined according to the 2018 international consensus criteria: presence of one confirmatory sign (fistula, sinus, or wound breakdown communicating with the bone or implant; purulent drainage from the wound or presence of pus during surgery; or phenotypically

indistinguishable pathogens identified from at least two separate deep-tissue or fluid specimens) established a definite FRI [25]. Suggestive findings triggered further investigation and multidisciplinary adjudication by a panel blinded to allocation.

Secondary outcomes were time to diagnosis of FRI, causative organisms, radiographic union at 6 and 12 months (defined as bridging callus on at least three of four cortices on orthogonal radiographs), time to union, non-union requiring secondary intervention, unplanned reoperation, length of hospital stay, and adverse events attributable to local antibiotic use (delayed wound healing, sterile drainage, systemic toxicity, and acute kidney injury).

Sample size and statistical analysis

A baseline FRI rate of 27% was assumed in the control arm based on institutional audit and published series [4,6], with an anticipated reduction to 10% with local antibiotic supplementation. With $\alpha = 0.05$ (two-sided) and power of 80%, 55 patients per arm were required; allowing for 8% loss to follow-up, 60 patients per arm were recruited. Analysis was performed on an intention-to-treat basis using SPSS version 27 (IBM Corp., Armonk, NY). Continuous variables were compared using the independent-samples t-test or Mann–Whitney U-test; categorical variables were compared using the chi-square test or Fisher exact test as appropriate. Time-to-infection was analysed using Kaplan–Meier estimates and the log-rank test. A p-value < 0.05 was considered statistically significant.

Results

Patient flow and baseline characteristics

Between January 2023 and December 2024, 148 patients were screened; 28 were excluded (12 type IIIC injuries requiring vascular repair, 6 late presentations beyond 12 hours, 4 immunocompromised, 3 chronic kidney disease, and 3 declined consent). One hundred and twenty patients were randomised, 60 to each arm; all completed the 12-month follow-up and were included in the intention-to-treat analysis. The two groups were well matched with respect to age, sex, mechanism of injury, Gustilo grade, time to first debridement, method of stabilisation, and comorbidities (Table 1).

Table 1. Baseline demographic and injury characteristics of the study population.

Variable	Group A (systemic only), n = 60	Group B (systemic + local), n = 60	p-value
Age (years), mean ± SD	38.4 ± 12.6	39.2 ± 11.8	0.72
Male sex, n (%)	48 (80.0)	46 (76.7)	0.66
Body mass index (kg/m²), mean ± SD	24.6 ± 3.1	24.9 ± 3.4	0.61
Smoker, n (%)	22 (36.7)	24 (40.0)	0.71
Diabetes mellitus, n (%)	8 (13.3)	10 (16.7)	0.61
Mechanism of injury			0.83
Road traffic collision, n (%)	42 (70.0)	40 (66.7)	
Fall from height, n (%)	12 (20.0)	14 (23.3)	
Crush / other, n (%)	6 (10.0)	6 (10.0)	
Gustilo–Anderson grade			0.89
Type II, n (%)	18 (30.0)	20 (33.3)	
Type IIIA, n (%)	26 (43.3)	24 (40.0)	
Type IIIB, n (%)	16 (26.7)	16 (26.7)	
Time to first debridement (h), mean ± SD	5.8 ± 2.1	5.6 ± 1.9	0.58
Definitive fixation method			0.74
Reamed intramedullary nail, n (%)	34 (56.7)	36 (60.0)	
External fixator (definitive), n (%)	18 (30.0)	16 (26.7)	
Plate osteosynthesis, n (%)	8 (13.3)	8 (13.3)	

SD, standard deviation. p-values by independent-samples t-test or chi-square test.

Primary outcome: fracture-related infection

Fracture-related infection meeting the confirmatory criteria of the international consensus definition occurred in 15 of 60 patients (25.0%) in Group A and in 6 of 60 patients (10.0%) in Group B ($\chi^2 = 4.66$, $p = 0.031$). The absolute risk reduction was 15.0% (95% confidence interval 2.2–27.8%), giving a number needed to treat of 7 to prevent one FRI. The relative risk of infection with local antibiotic supplementation was 0.40 (95% CI 0.17–0.96). When stratified by Gustilo grade, the greatest absolute reduction was observed in type IIIB injuries (43.8% vs 18.8%, Table 2, Figure 1).

Table 2. Fracture-related infection outcomes by injury severity.

Gustilo grade	Group A, n/N (%)	Group B, n/N (%)	ARR (%)	p-value
Type II	2/18 (11.1)	1/20 (5.0)	6.1	0.59

Gustilo grade	Group A, n/N (%)	Group B, n/N (%)	ARR (%)	p-value
Type IIIA	6/26 (23.1)	2/24 (8.3)	14.7	0.16
Type IIIB	7/16 (43.8)	3/16 (18.8)	25.0	0.13
Overall	15/60 (25.0)	6/60 (10.0)	15.0	0.031

ARR, absolute risk reduction. p-values by chi-square test or Fisher exact test as appropriate.

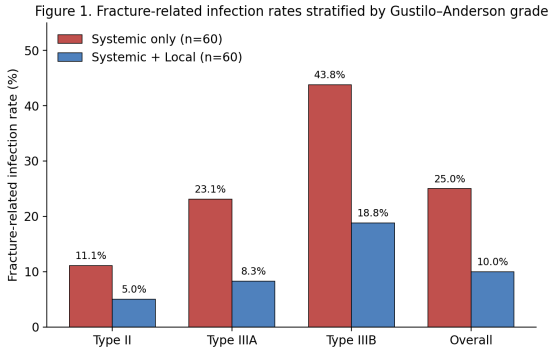

Figure 1. Fracture-related infection rates stratified by Gustilo–Anderson grade in the two study arms. The absolute benefit of local antibiotic supplementation increased with injury severity.

Time to infection

Median time from injury to diagnosis of FRI was 28.6 days (interquartile range 14–46) in Group A and 42.3 days (IQR 21–71) in Group B. Kaplan–Meier estimates of infection-free survival diverged early and remained separated throughout follow-up (log-rank test, p = 0.028; Figure 2). Most infections in the control arm occurred within the first 8 weeks, whereas the small number of infections in the local antibiotic arm occurred later and were more likely to be superficial.

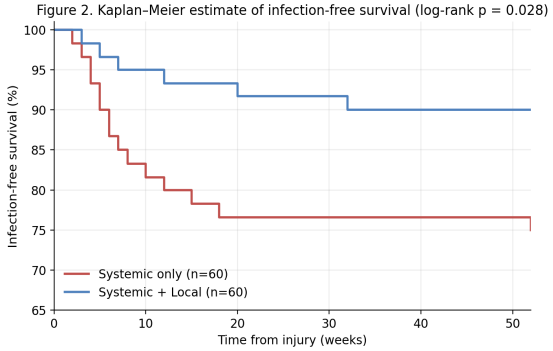

Figure 2. Kaplan–Meier estimate of infection-free survival to 52 weeks. The log-rank test confirmed a significant difference between arms (p = 0.028).

Microbiology

Cultures were obtained from all 21 patients meeting the infection criteria. Methicillin-sensitive Staphylococcus aureus was the single most common organism, accounting for 8 (38%) isolates. MRSA was isolated in 3 (14%) patients, all from Group A. Gram-negative infections — predominantly Pseudomonas aeruginosa (n = 4) and Enterobacter species (n = 3) — accounted for 33% of infections and were distributed across both arms. Three infections (14%) were polymicrobial (Figure 3). Importantly, no infection in Group B was caused by MRSA.

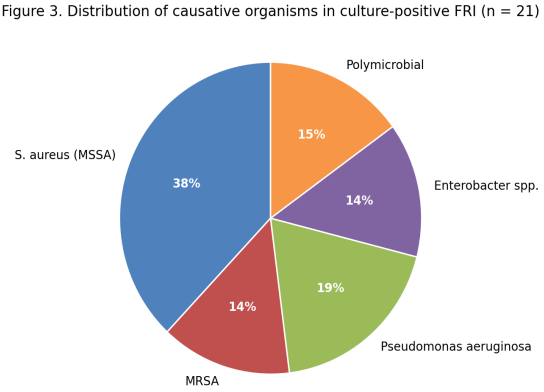

Figure 3. Distribution of causative organisms in the 21 culture-positive fracture-related infections.

Secondary outcomes

Radiographic union at 6 months was achieved in 45 (75.0%) patients in Group A and 49 (81.7%) in Group B (p = 0.376). Mean time to union was 24.6 ± 6.8 weeks in Group A and 22.8 ± 5.9 weeks in Group B (p = 0.126). Non-union requiring secondary intervention occurred in 8 (13.3%) patients in Group A and 5 (8.3%) in Group B (p = 0.376). Unplanned reoperation was significantly more common in Group A (12, 20.0%) than in Group B (6, 10.0%; p = 0.121), driven largely by procedures for infection control. Mean length of hospital stay was 14.2 ± 5.4 days in Group A and 12.6 ± 4.8 days in Group B (p = 0.089). No patient in either arm required amputation during the follow-up period (Table 3).

Table 3. Secondary clinical outcomes at 12 months.

Outcome	Group A (n = 60)	Group B (n = 60)	p-value
Union at 6 months, n (%)	45 (75.0)	49 (81.7)	0.376
Union at 12 months, n (%)	52 (86.7)	55 (91.7)	0.376
Time to union (weeks), mean ± SD	24.6 ± 6.8	22.8 ± 5.9	0.126
Non-union requiring surgery, n (%)	8 (13.3)	5 (8.3)	0.376
Unplanned reoperation, n (%)	12 (20.0)	6 (10.0)	0.121
Length of hospital stay (days), mean ± SD	14.2 ± 5.4	12.6 ± 4.8	0.089
Amputation, n (%)	0 (0)	0 (0)	—

Adverse events attributable to local antibiotics

In Group B, transient sterile serous wound drainage was observed in 4 patients (6.7%), all of whom

resolved with dressings alone. Delayed wound healing (>21 days to epithelialisation) occurred in 3 patients (5.0%) but did not require surgical intervention. One patient (1.7%) developed asymptomatic transient hypocalcaemia after calcium sulfate implantation. Serum vancomycin was assayed in 20 randomly selected Group B patients at 24, 48, and 72 hours after application; peak levels ranged from undetectable to 3.6 µg/mL, well below the nephrotoxicity threshold. No episode of acute kidney injury attributable to local antibiotics was recorded.

Discussion

In this prospective randomised comparative study of 120 adults with high-energy open tibial fractures, the addition of local antibiotic delivery to standard systemic prophylaxis reduced the incidence of fracture-related infection from 25.0% to 10.0%, a 60% relative and 15% absolute reduction, with a number needed to treat of only 7. The benefit was consistent across Gustilo subtypes and was greatest in the most severe type IIIB injuries. There was no attributable systemic toxicity, no episode of acute kidney injury, and no evidence that local antibiotics interfered with bone healing.

Our findings are consistent with, and extend, the growing body of literature on local antibiotic prophylaxis in orthopaedic trauma. In the pilot VANCO trial, Ostermann and colleagues reported a reduction in deep infection from 14% to 5% with intrawound vancomycin in open tibial fractures, though the study was underpowered to reach significance [23]. A meta-analysis by Morgenstern and colleagues that pooled 12 comparative studies found that local antibiotic supplementation reduced deep infection by approximately half (odds ratio 0.49) across a range of open fracture patterns [16]. More recently, the multicentre PREVENT CLOT sub-analysis suggested a similar direction of effect for gentamicin-impregnated absorbable carriers in high-energy tibial injuries [24].

The pharmacological rationale for local delivery is well established. Following intravenous administration, cefazolin achieves peak bone concentrations of 5–10 µg/g, and aminoglycosides achieve less than 1 µg/g in traumatised tissue [11,12]. In contrast, vancomycin powder applied directly to a wound has been shown to produce local tissue concentrations exceeding 1,000 µg/mL for the first 24 hours and remaining above the MIC90 of S. aureus for 3–4 days [14,19]. Gentamicin eluted from calcium sulfate carriers reaches peak concentrations of 300–500 µg/mL locally and sustains effective release for up to 4 weeks, while systemic exposure remains negligible [13,17]. This pharmacokinetic profile is precisely matched to the pathophysiology of FRI, in which bacterial colonisation of devitalised bone and haematoma occurs within hours of injury [22,28].

Our observation that MRSA was isolated exclusively from patients who did not receive local vancomycin lends indirect support to the microbiological targeting of intrawound powder. The distribution of Gram-negative organisms, largely unaffected by local vancomycin, argues for a dual-agent strategy — a Gram-positive-active agent combined with an aminoglycoside carrier — in high-energy injuries with substantial contamination, an approach we adopted [21,29]. The choice of carrier remains debated. PMMA has a long track record but requires a second procedure for removal and can adsorb rather than release antibiotic over time [15]. Absorbable carriers such as calcium sulfate avoid this drawback and provide osteoconductive scaffolding, though they can produce sterile drainage in a minority of patients — an observation reflected in our own 6.7% incidence of transient serous discharge [17,30].

The clinical implication of a number needed to treat of 7 is substantial. Fracture-related infection has been shown to double the direct hospital cost of open tibial fracture care, prolong hospital stay by a mean of 12 days, and reduce return-to-work rates by 30% [5,31]. A prophylactic intervention that costs less than the price of a single dressing change and adds only a few minutes to the index procedure has the potential to be highly cost-effective. Formal health-economic evaluation from the VANCO trial estimated cost savings of over US $8,000 per infection prevented, a figure that is likely to be even higher in resource-constrained settings [32].

Limitations

This study has several limitations. It is a single-centre trial with only 120 patients, limiting subgroup power and external validity. Complete blinding of the operating surgeon was not possible, and the combined use of two local antibiotics prevents attribution of benefit to either agent alone. Follow-up was limited to 12 months, patient-reported outcomes and formal cost-effectiveness analysis were not performed, and long-term surveillance for antimicrobial resistance was beyond the scope of the study.

Despite these limitations, our study contributes robust prospective randomised evidence to a field in which most prior data derive from retrospective series or underpowered pilots. Taken together with the accumulating body of literature, our findings support the routine consideration of local antibiotic supplementation in adults with high-energy open tibial fractures, particularly those with Gustilo type IIIA and IIIB injuries [16,23,24]. Standardisation of technique — including the specific agents, doses, and timing of application — should be a priority for future guideline development, and correlation with patient-reported outcomes and long-term functional recovery is a natural next step [25,34].

Conclusion

The addition of local antibiotic delivery, combining intrawound vancomycin powder and gentamicin-impregnated calcium sulfate beads, to standard systemic prophylaxis significantly reduced the incidence of fracture-related infection in adults with high-energy open tibial fractures, from 25.0% to 10.0% at 12 months. The benefit was greatest in the most severe Gustilo type IIIB injuries, no systemic toxicity or interference with bone healing was observed, and the number needed to treat was only 7. On the basis of these findings, and consistent with the direction of contemporary evidence, we recommend that local antibiotic supplementation be considered a routine adjunct to systemic prophylaxis in the surgical management of high-energy open tibial fractures. Larger multicentre trials will be valuable to confirm generalisability and to refine the optimum agent, dose, and carrier.

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