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Gentamicin-Coated Tibia Nail in Fractures and Nonunion to Reduce Fracture-Related Infections: A Systematic Review

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ABSTRACT
Open tibial fractures and nonunion cases carry a high risk of fracture-related infections (FRI), often requiring advanced strategies to mitigate complications. Gentamicin-coated intramedullary nails have been proposed as a localized antibiotic delivery system to prevent infections without systemic side effects. This systematic review aimed to evaluate the efficacy and safety of gentamicin-coated tibial nails in fracture fixation (FF) and revision surgeries (RS) for nonunion, with a specific focus on FRI incidence, healing outcomes and adverse effects. A systematic search of PubMed, Cochrane and EMBASE databases was conducted following PRISMA guidelines. Studies were selected based on predefined inclusion criteria, with data extracted and analyzed from eight eligible studies comprising 203 patients. Outcomes assessed included FRI incidence, superficial surgical site infections (SSI), bone healing, nonunion rates and reoperation requirements. Among 114 FF cases, 63% were open fractures and the FRI rate was 3.81%. Bone healing was achieved in 76.2%, with nonunion in 5.7%. In the RS group (n=89), which included 43% infected nonunion cases, the FRI rate was 6.49%, bone healing occurred in 83.1% and nonunion persisted in 11.7%. No systemic adverse effects related to gentamicin were reported in either group. Gentamicin-coated tibial nails demonstrate promising efficacy in reducing FRI rates, particularly in high-risk open fractures and nonunion cases. Their favorable safety profile and local antibiotic delivery mechanism support their clinical utility, although further high-quality randomized trials are warranted to confirm these findings and refine indications.

INTRODUCTION

Tibial shaft fractures represent the most prevalent type of long-bone fractures in both adults and children, with significant implications for individual health and healthcare systems. Epidemiological data estimate an incidence of approximately 26 fractures per 100,000 individuals annually, contributing to a substantial healthcare burden of nearly 569,000 hospital days per year. Men are disproportionately affected, with a threefold increased risk compared to women. The injury patterns vary across age groups high-energy trauma being the predominant cause in younger adults, while elderly individuals often sustain such fractures from low-energy mechanisms due to compromised bone quality associated with osteoporosis[1]. Among tibial fractures, open fractures pose a particularly formidable challenge due to their high susceptibility to infection. These injuries can account for as many as 2 per 1000 total injuries and in elderly patients, the incidence of open tibia fractures reaches up to 30%, with approximately 10% resulting in nonunion and 17% in malunion. Nonunion itself is a major complication, occurring in approximately 12% of tibial shaft fractures in the general population, with an even higher rate (up to 23%) in open fractures[2]. Fracture-related infection (FRI) is a serious and potentially debilitating complication associated with tibial fractures, particularly in open and complex cases. It is estimated that 64% of all FRIs involve the tibia, making it the most infection-prone anatomical site among long bones. These infections significantly increase treatment duration, patient morbidity and healthcare expenditures, with costs escalating up to 6.5 times in affected cases[3]. The current gold standard for infection prevention includes meticulous surgical debridement and systemic antibiotic prophylaxis. However, systemic antibiotics are often insufficient in fully preventing implant-associated infections due to biofilm formation a defense mechanism in which bacteria adhere to implant surfaces and are shielded from systemic antibiotics by a protective extracellular matrix. Biofilm-associated infections are notoriously resistant to eradication and represent a major reason for surgical failure in fracture management[4]. To address these limitations, antibiotic-coated implants have emerged as a novel strategy to enhance local antibiotic delivery while minimizing systemic toxicity. Among these, the gentamicin-coated intramedullary tibial nail (ETN PROtect™, DePuy Synthes) has gained particular attention. This implant consists of a titanium alloy coated with an absorbable poly (d,l-lactide) (PDLLA) matrix impregnated with gentamicin sulfate. The design facilitates a biphasic release of gentamicin, with an initial burst release of approximately 40% within the first hour post-implantation, followed by sustained release as the polymer degrades. The coating process preserves the structural integrity of both the gentamicin and the PDLLA, ensuring their functionality[5]. The ETN PROtect™ nail is recommended in clinical scenarios with elevated infection risk, including Gustilo-Anderson grade I-III open fractures, revision surgeries following prior infection, polytrauma and immunocompromised states. Despite growing clinical use, robust evidence supporting its efficacy and safety remains limited, with relatively few studies directly comparing outcomes between coated and uncoated implants[6]. Given this background, the present systematic review was conducted to comprehensively assess the current evidence on the clinical utility of gentamicin-coated tibial nails. The primary objective was to evaluate their efficacy in reducing the incidence of fracture-related infections in both primary fracture fixation and revision surgery for nonunion. Secondary objectives included analysis of bone healing rates, nonunion persistence, surgical complications and adverse effects associated with gentamicin use. By synthesizing data across available clinical studies, this review aims to guide evidence-based decision-making in orthopedic trauma care involving high-risk tibial fractures.

MATERIALS AND METHODS

This systematic review was conducted to evaluate the clinical outcomes associated with the use of gentamicin-coated intramedullary tibial nails in patients undergoing primary fracture fixation or revision surgeries for nonunion. A comprehensive literature search and analysis were performed in accordance with a predefined protocol, incorporating clearly stated objectives and inclusion criteria. A detailed and exhaustive search was carried out using three major biomedical databases-PubMed, EMBASE and the Cochrane Library. The literature search was limited to studies published in the English language after January 2000. The keywords and medical subject headings (MeSH terms) used for the search strategy included combinations of "antibiotic coating," "intramedullary nail," "tibia fractures," "nonunion" and "gentamicin-coated nails." Boolean operators such as "AND" and "OR" were used to refine the search to ensure comprehensive capture of relevant studies. Additionally, the reference lists of all included articles were manually screened to identify any further eligible studies that may not have been retrieved in the initial search. Two independent reviewers assessed all retrieved titles and abstracts for potential relevance. Studies that met the initial screening criteria were retrieved in full and evaluated for eligibility.

Inclusion Criteria were as Follows:

- Original clinical studies (including case reports, case series, case-control studies, cohort studies, and randomized controlled trials).

- Studies that involved human subjects undergoing tibial fracture fixation or revision surgery with the use of gentamicin-coated nails.
- Studies reporting clear outcome data on the incidence of fracture-related infection (FRI), bone healing, nonunion, superficial surgical site infection (SSI), reoperation and follow-up duration. Exclusion criteria included animal studies, in vitro experimental studies, review articles and studies lacking sufficient clinical outcome data.

Any discrepancies in study selection were resolved through consensus discussion with a third senior reviewer. Once the final set of included studies was confirmed, the level of evidence of each study was determined based on the Oxford Centre for Evidence-Based Medicine classification system. From each eligible study, detailed data were systematically extracted. These included the number of patients, study design, age, sex distribution, comorbid conditions (e.g., diabetes, smoking, alcohol use), trauma type (polytrauma vs. isolated fracture), fracture classification using Gustilo-Anderson grading, indication for surgery (primary fixation vs. revision), use of adjunctive procedures (e.g., bone grafting or Masque let technique) and type of implant used.

Patients were Categorized into Two Groups Based on the Indication for Coated Nail Use:

- Fracture fixation group (FF), defined as patients who received gentamicin-coated intramedullary nails within four weeks of trauma.
- Revision surgery group (RS), comprising patients undergoing secondary procedures for nonunion (infected or aseptic) after previous surgical management.

Outcomes of interest included the incidence of FRI (defined according to the European Bone and Joint Infection Society consensus), superficial SSI, complete and partial bone healing, nonunion at last follow-up and requirement for additional surgical interventions (including reoperation or nail dynamization). Studies that reported laboratory parameters, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), leukocyte counts and imaging findings were also considered when evaluating infection outcomes. Duration of follow-up was recorded where available. Quantitative data were analyzed using descriptive and inferential statistical methods. Statistical analysis was performed using R software version 3.4.4 (R Core Team, 2018). Continuous variables were expressed as mean±standard deviation and categorical variables as absolute numbers and percentages. For group comparisons, the t-test was used for continuous variables and Fisher's exact test for categorical data. A two-sided p-value of <0.05 was considered statistically significant and 95% confidence intervals were calculated where applicable.

RESULTS AND DISCUSSIONS

The findings of this systematic review are based on eight eligible studies comprising a total of 203 patients who received gentamicin-coated tibial nails for either recent fractures or revision surgeries for nonunion. The analysis compares clinical outcomes, including infection rates and healing patterns, between the fracture fixation (FF) and revision surgery (RS) groups. No statistically significant differences were found between the groups regarding the incidence of FRI, nonunion, or healing outcomes. **(Table 1)** demonstrates the demographic and clinical characteristics of the included population, segregated by surgical indication.

Table 1: Distribution of Demographic and Clinical Features in Fracture Fixation and Revision Surgery Groups

Variable	Fracture Fixation (n=114)	Revision Surgery (n=89)	Total (N=203)
Mean Age (years)	45.7 ± 13	45.3±13	45.5±13
Female Sex	28 (24.6%)	25 (28.1%)	53 (26.1%)
Smokers	18 (15.8%)	26 (29.2%)	44 (22.2%)
Alcohol Use	0	22 (24.7%)	22 (10.8%)
Diabetes Mellitus	1 (0.9%)	8 (9.0%)	9 (4.4%)
Polytrauma Cases	22 (19.3%)	17 (19.1%)	39 (19.2%)
Open Fractures	72 (63.2%)	62 (69.7%)	134 (66.0%)
Infected Nonunion Cases	–	25 (28.1%)	25 (12.3%)

(Table 2) illustrates the clinical outcomes observed in the fracture fixation group. Most fractures were open (63.2%) and the FRI rate was 3.81%. Bone healing was achieved in 76.2% of cases, while nonunion was seen in 5.7%.

Table 2: Clinical Outcomes in the Fracture Fixation Group (n=114)

Outcome Parameter	n (%)
Closed Fracture	42 (36.8%)
Open Fracture (All GA grades)	72 (63.2%)
• GA I	20 (17.5%)
• GA II	23 (20.2%)
• GA IIIa–IIIc (combined)	52 (45.6%)
Fracture-Related Infection (FRI)	4 (3.81%)
• Closed Fracture FRI	1 (0.95%)
• Open Fracture FRI	3 (2.86%)
Superficial SSI	3 (2.86%)
Bone Healed	80 (76.2%)
Partial Healing	19 (18.1%)
Nonunion at Follow-up	6 (5.7%)
Reoperation (excluding dynamization)	8 (7.6%)
Nail Dynamization	25 (23.8%)
Median Follow-up (months)	14 ± 7

(Table 3) summarizes the outcomes in the revision surgery group. This group included 64 nonunion cases (71.9%), with an FRI incidence of 6.49%. Bone healing was reported in 83.1% of patients and persistent nonunion was observed in 11.7%.

Table 3: Clinical Outcomes in the Revision Surgery Group (n=89)

Outcome Parameter	n (%)
Nonunion	64 (71.9%)
Infected Nonunion	25 (28.1%)
Previous Closed Fracture	27 (30.3%)
Previous Open Fracture	62 (69.7%)
• GA I–III (combined)	57 (64.0%)
FRI (Total)	5 (6.49%)
• Relapse in Infected Nonunion	4 (4.5%)
• New Onset in Aseptic Nonunion	1 (1.1%)
Superficial SSI	9 (11.7%)
Bone Healed	64 (83.1%)
Partial Healing	4 (5.2%)
Nonunion at Follow-up	9 (11.7%)
Reoperation	6 (7.8%)
Nail Dynamization	2 (2.6%)
Median Follow-up (months)	13.9 ± 3.5

(Table 4) presents the comparative statistical analysis between the FF and RS groups. No statistically significant differences were observed in the key outcome parameters.

Table 4: Comparative Analysis Between Fracture Fixation and Revision Surgery Groups

Variable	FF Group (n=114)	RS Group (n=89)	p-value
Fracture-Related Infection	3.8%	6.5%	0.0642
Bone Healing Rate	76.2%	83.1%	0.2745
Nonunion at Follow-up	5.7%	11.7%	0.1773

(Table 5) presents the association between Gustilo -Anderson (GA) classification and the incidence of fracture-related infections (FRI) in the fracture fixation group. Although a higher trend of infection was observed in GA III fractures, the difference was not statistically significant.

Table 5: Association of Gustilo-Anderson Classification with FRI in Fracture Fixation Group (n=114)

GA Classification	Total Cases	FRI Cases	FRI Rate (%)
Closed Fractures	42	1	2.38%
GA I	20	0	0.00%
GA II	23	0	0.00%
GA III (combined)	52	3	5.77%
p-value (Closed vs. Open)	–	–	1.000

(Table 6) summarizes the functional outcomes reported in studies that evaluated patient-reported scores using the SF-36 physical and mental health domains. These were limited to two studies within the fracture fixation group.

Table 6: Functional Outcome Scores (SF-36) in Fracture Fixation Group

Study	SF-36 Physical	SF-36 Mental
Fuchs *et al.* (2011)	42.55	50.45
Schmidmaier *et al.* (2017)	44.60	53.10

(Table 7) outlines the adjunctive procedures used in revision surgeries for nonunion management. These included the use of the Masque let technique and Reaming Irrigation and Aspiration (RIA) system, both aimed at enhancing bone regeneration and infection control.

Table 7: Adjunctive Procedures Used in Revision Surgery Group (n=89)

Adjunctive Method	Number of Patients	Percentage (%)
Bone Grafting (RIA or Autologous)	29	32.6%
Masque let Technique (Second Stage)	12	13.5%
No Adjunctive Procedures Reported	48	53.9%

The findings of this systematic review highlight the potential of gentamicin-coated tibial nails in addressing two of the most challenging complications in orthopedic trauma surgery: fracture-related infection (FRI) and nonunion. Although the overall difference in FRI incidence between the fracture fixation (FF) and revision surgery (RS) groups did not reach statistical significance, there was a trend favoring lower infection rates in the FF group (3.81% vs. 6.49%). This is clinically relevant given the high baseline risk of infection in open tibial fractures, particularly Gustilo-Anderson grade III injuries, which accounted for nearly half of all open fractures in the FF cohort[7,8]. The observed FRI rates in both groups are favorable compared to historical controls using uncoated intramedullary nails. According to the Swedish Fracture Register, the average infection rate in tibial fractures treated with standard nails was 3.4%, with a higher nonunion rate of 8.1%. The bone healing rates in the current review (76.2% in FF and 83.1% in RS) align closely with or surpass those historical rates, suggesting that gentamicin-coated implants may contribute not only to infection prevention but also to overall improved healing outcomes in complex cases[9]. Particularly noteworthy is the difference in FRI recurrence in the RS group between patients with aseptic nonunion and those previously infected. Of the five FRI cases in this group, four occurred in patients with a prior infection[10]. This statistically significant association (p=0.0208) underlines the difficulty in managing previously infected nonunions, even with coated implants. Nonetheless, the overall healing rate in the RS group was high and the majority of patients did not require re-operation, suggesting that the local antibiotic environment provided by the coating may play a protective role during the reconstructive phase. The application of the Masque let technique and bone grafting in revision surgeries further enhanced outcomes. In over 30% of RS cases, adjunctive biological strategies were employed, often in tandem with the coated implant, particularly in atrophic nonunion and bone defect scenarios[11,12]. This reflects current trends in the literature supporting the combination of local antibiotic delivery and bone regenerative strategies as part of a “diamond concept” approach to nonunion. When examining functional outcomes, only two studies reported SF-36 scores, both of which demonstrated acceptable physical and mental health scores in the mid-40s to low 50s range[13]. While limited, these findings suggest that gentamicin-coated nails do not impair long-term function, though more patient-reported outcome measures are needed to fully assess this aspect. From a safety perspective, no systemic toxicity associated with gentamicin was reported. Previous pharmacokinetic studies indicate that gentamicin release from coated implants remains below the detectable threshold for systemic toxicity (0.2 mg/dL). Importantly, the localized release does not appear to compromise bone healing, which has been a concern with high local antibiotic concentrations in other delivery systems[14,15]. In this review, no adverse events were directly attributed to the gentamicin coating, further supporting its favorable safety profile. The limitations of this review are rooted in the heterogeneity and relatively low evidence level of included studies. Most were case series or reports, with only one randomized study (Pinto *et al*.) offering comparative data. Additionally, differences in diagnostic definitions for infection, inconsistent follow-up protocols and variation in systemic antibiotic regimens across studies limit direct comparability. Not all studies used standardized biomarkers or imaging for infection surveillance, which may have led to under reporting or mis classification. Despite these constraints, this review synthesizes the largest body of evidence to date on the clinical utility of gentamicin-coated tibial nails in both primary and revision orthopedic trauma surgery. The findings support their use in high-risk cases, particularly open fractures and infected nonunions, where conventional strategies may be insufficient.

CONCLUSION

Gentamicin-coated intramedullary tibial nails appear to offer a clinically meaningful benefit in reducing fracture-related infections, particularly in open fractures and revision surgeries for nonunion, including those with prior infections. The localized antibiotic release system provides effective prophylaxis without systemic toxicity, while maintaining favorable bone healing outcomes. Although evidence from high-level randomized trials remains limited, the current findings support the selective use of gentamicin-coated nails in patients at elevated risk of infection or with a history of prior septic complications. Future large-scale, controlled studies are needed to further define indications, long-term safety and cost-effectiveness.

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