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ORIGINAL ARTICLE

A major trauma centre experience with gentamicin-coated tibial intramedullary nails (ETN PROtect™) in acute primary open fracture fixation and complex revision surgery

Kavi H. Patel[1] · Athanasios Galanis[2] · Prabu Balasubramanian[1] · Alexios D. Iliadis[1] · Nima Heidari[1] · Alex Vris[1]

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Abstract

Purpose Fracture-related infections (FRI) following intramedullary nailing for tibial shaft fractures remain challenging to treat with associated high patient morbidity and health care costs. Recently, antibiotic-coated nails have been introduced as a strategy to reduce implant related infection rates in high-risk patients. We present the largest single-centre case series on ETN PROtect® outcomes reporting on fracture union, infection rates and treatment complications.

Methods Fifty-six adult patients underwent surgery with ETN PROtect® between 01/09/17 and 31/12/20. Indications consisted of acute open fractures and complex revision cases (previous FRI, non-union surgery and re-fracture) with a mean of three prior surgical interventions. We report on patient demographics, union rates and deep infection. Minimum follow-up was one year.

Results One (1.8%) patient developed a deep surgical infection and associated non-union requiring further surgery. In addition, we identified three cases (5.4%) of aseptic non-union following facture treatment with ETN PROtect®. Of the five patients who underwent staged complex revision surgery for established FRI with ETN PROtect®, all had treatment failure with ongoing symptoms of deep infection requiring implant removal and further treatment.

Conclusion Use of the ETN PROtect® nail in high-risk patients (open fractures and those initially treated with external fixation) and in those patients with aseptic non-unions, demonstrates promising outcomes in the prevention of implant-related infection. In our limited series we have failed to observe any benefit over uncoated nails, when used in treating cases of previously established FRI/osteomyelitis and would therefore advise caution in their use, especially in view of the high cost.

Keywords Bone infection · Tibia · Open fractures · Antibiotic coating · Intramedullary nailing

Introduction

The treatment of fracture related infections (FRI) following intramedullary nailing for tibial shaft fractures poses a major challenge and is associated with high patient morbidity and health care-related costs [1]. The tibia, with its specific anatomical features, remains the area at highest risk of infection with 64% of all FRIs located in this region [2]. The risk of developing post-traumatic deep infection is multifactorial with reported rates of between 1% following operative fixation of simple closed fractures to 30% in Gustilo–Anderson type III open fractures of the tibia [3, 4]. Other risk factors are known to include morbid obesity, diabetes, smoking and high injury severity scores [5]. Furthermore, higher infection rates have been reported in cases of intramedullary nailing following a period of external stabilisation and a non-union rate of up to 23% has been suggested in another study [6, 7].

Currently, the prevention of FRI following open tibial fractures involves early systemic antibiotic administration and appropriate ortho-plastics surgical management as per British Orthopaedic Association Standards for Trauma (BOAST 4) [8]. Systemic antibiotic prophylaxis has recognised limitations since bacteria form a shielding biofilm at implant level which hinders antibiotic penetration [9]. Additionally, systemic antibiotics may result in side effects and delivery can be impaired in traumatised and ischaemic

✉ Kavi H. Patel
kavi.patel@nhs.net

[1] Limb Reconstruction and Bone Infection Service, The Royal London Hospital, Barts Health NHS Trust, Whitechapel Road, London E1 1FR, UK

[2] KAT General Hospital, Nikis 2, 145 61 Kifisia, Greece

tissue. Antibiotic-coated nails, which have the advantage of combining a fracture fixation device with a way of delivering a high concentration of local antibiotics rapidly, have been introduced in recent years as a strategy to reduce implant-related infection rates in high-risk patients. Their use in open tibial fractures has been supported in the literature with reported high rates of fracture union and reduction of infection rates [10, 11]. We present the largest single-centre case series on gentamicin-coated nails (ETN PROtect™, DePuy Synthes) in our cohort of high-risk patients with either primary tibial fractures or complex revision cases. Our aim was to report on treatment outcomes defined as fracture union, infection rates and complications.

Materials and methods

This is a retrospective case series from the UK Major Trauma Centre. Institutional approval was obtained prior to the study. Consecutive adult patients treated with the ETN PROtect™ nail at the Royal London Hospital (Barts Health NHS Trust) over a 4-year period (1st January 2017–31st December 2020) were identified using theatre implant records. Patient data were recorded at admission on our electronic hospital database and retrospectively evaluated for this study to include patient demographics and co-morbidities, indication for implant use (including injury classification and underlying pathology), mean number of surgeries, adverse events, union time and infection rates. All open fractures were managed as per BOAST 4 and classified according to the Gustilo–Anderson (GA) classification. Informed consent was obtained in all patients except when state of consciousness did not allow (intubation following polytrauma).

ETN PROtect™ is a titanium alloy intramedullary tibial nail coated in poly-lactide (PDLLA) containing gentamicin. All surgical procedures were performed in accordance with standard practice and manufacturers' guidance (Expert TN – Technique, DSEM/TRM/0316/0625) [12]. Indications for the use of ETN PROtect™ include cases at high risk of infection, for example, in polytraumatised or immunosuppressed patients, in patients with open fractures and in patients with complications such as non-unions requiring revision procedures. The implant manufacturers advise against its use in the presence of established infection. Exclusion criteria consist of pregnant or breastfeeding women and skeletally immature patients.

Fracture union was evaluated both clinically (absence of tenderness over fracture site on palpation and absence of pain on weight bearing) and radiologically at follow-up (bridging callus at three cortices on conventional AP and lateral radiographs) by two senior orthopaedic surgeons independently. Non-union was considered as cessation of healing on consecutive radiographs after at least 6 months with the expectation that consolidation would not be achieved without further intervention. Infection was defined by the criteria described in the international expert consensus on FRI [13]. Follow-up protocol was standardised with visits at two weeks, six weeks, three months, six months and one year post-operatively although there was slight variation to this depending on clinic/patient availability.

Descriptive statistics for means, ranges and frequency are provided. All treated patients have been included in the analysis. Statistical significance was performed using unpaired *t* test (GraphPad Software Inc, San Diego, CA, USA), and a P value < 0.05 was considered significant.

Results

Patient demographics and treatment indications are presented in Table 1. Fifty-six patients were included in this study of which 51 had a minimum of one year follow-up in our institution. The remaining five patients were re-patriated back to their local units which were contacted and provided 12-month outcome data for them to be included in our study. Indication for surgery was acute primary fracture fixation in 38 patients and complex revision surgery in 18 patients. All patients in the primary fixation group had open fractures, of which 54.9% were severe (GA type 3). Importantly, 26.8% of our patients were polytraumatised and 47.4% were initially treated in an external fixator. The mean number of surgeries prior to treatment with ETN PROtect™ was 1.6 (range; 0–5). A total of 28 patients underwent concomitant plastic surgery procedures of which there were 23 local or free flaps and 5 split thickness skin grafts.

Of the revision cases, five were performed following non-union in previously treated cases of FRI, 12 for aseptic non-unions and one following a re-fracture. The majority of non-union cases (11/12) were following circular frame treatment in patients with complex tibia fractures with associated extensive soft tissue injuries and/or bone loss. The remaining case was in a tibial fracture initially treated with a standard nail who underwent exchange nailing with ETN PROtect™. The patient with a re-fracture had a fall three months following circular frame removal (after successful treatment of a closed tibial fracture).

Mean fracture union time was 27.7 weeks (range; 16–64) and there was no statistically significant difference observed between primary and complex revision surgery. Whilst over 30% of patients were smokers none were found in the non-union group (either primary or complex revision). Three patients with acute fractures treated with ETN PROtect™ developed an aseptic non-union requiring further surgical intervention. Union was achieved in all cases where the implant was used in the context of previous established

Table 1 Summary of Cases

Demographics		
Mean age (years)	Males	Females
43.3	44 (78.6%)	12 (21.4%)
Injury		
Polytrauma	Gustilo–Anderson Grade	Fasciotomy
15 (26.8%)	1 16	2 (3.6%)
Open	2 7	
51 (91.1%)	3A 8	Plastic Surgery
Initial external fixation	3B 20	28 (50%)
18 (47.4%)	3C 0	
Co-morbidities		
Diabetes	Smoking	Drug/alcohol abuse
3 (5.4%)	17 (30.4%)	5 (8.9%)
Indication for Surgery		
Primary trauma	Complex revision	
38 (67.9%)	18 (32.1%)	
Outcomes in acute open fracture group		
Infection	Non-union	Mean union time (weeks)
1 (1.8%)	3 (7.9%)	26.6
Outcomes in revision surgery group		
Septic non-union (infection relapse)		Mean union time (weeks)
5 (100%)		28.4

aseptic non-union revision surgery and no infections were observed in this group. One patient treated with ETN PROtect™ developed a deep infection. This was a 47-year-old male with an acute GA type 1 distal tibia fracture and a contralateral closed femoral fracture. Following external fixation, wound debridement and closure within 24 h of admission he underwent ETN PROtect™ nailing 8 days later. He was followed-up at his local hospital and re-referred to us 7 months later with an infected non-union and discharging sinus. Further intervention was at a different unit due to aggressive behaviour. Deep vein thrombosis was diagnosed and treated in two patients following ETN PROtect™ nailing in our cohort.

All patients treated with ETN PROtect™ in the context of FRI revision surgery eventually required implant removal due to ongoing infection and further stabilisation of non-union with a circular frame (Table 2). Prior to ETN PROtect™ treatment, all patients had been managed appropriately with removal of metalwork, bone/soft-tissue debridement, provision of a healthy soft tissue envelope and local/systemic antibiotics through a dedicated multidisciplinary bone infection service.

Discussion

Infections following tibial fracture fixation remain difficult to manage and are associated with increased hospitalisation and socio-economic impact. A study looking into the financial burden of infections following tibial shaft fractures

Table 2 Cases where ETN PROtect™ used for non-union following previous FRI treatment

Cases	Index procedure	Secondary procedures prior to ETN PROtect™	Organism	Open/closed
61 M	Tibial plate fixation	RoM, debridement and flap	Staph aureus / Group G strep	Closed
71 M	Tibial plate fixation	RoM, debridement, monorail fixator and flap	Staph aureus / Enterobacter cloacae	Closed
44 M	Intramedullary nail	RoM, SSG, Cerament-G	Staph epidermidis	Open (3B)
31 M	Uni-lateral fixator	Fixator removal and pin-site holiday	Staph aureus	Open (1)
58 M	Circular frame	Frame removal and pin-site holiday	Staph aureus	Open (3B)

RoM, removal of metalwork

found significantly increased inpatient costs, length of stay, re-admissions and re-operations associated with tibial FRI and that the burden could be reduced through novel surgical site infection prevention strategies [14]. A meta-analysis by Craig et al. has shown infection rates to drop from over 31% with systemic antibiotics only to under 9% with the addition of local antibiotics in severe cases (GA III B/C) [3]. One relatively recent innovation to reduce infection rates has been the use of antibiotic coated intramedullary nails to increase early local antibiotic delivery to address the sequelae of colonisation, biofilm formation and deep infection.

Several studies have reported on the benefit of antibiotic-coated nails with a recent systematic review demonstrating a reduction in infection rates of up to 75% in high-risk patients [15, 16]. In view of the significant cost difference, with a retail price of more than three times that of a standard nail, their use must be justified. Pinto et al., one of only two randomised studies in the literature comparing antibiotic coated and uncoated tibial nails, showed a statistically significant lower incidence of FRI in the coated group ($P = 0.031$) [17].

We investigated all patients retrospectively who had ETN PROtect™ at our centre over a 4-year period. The majority of patients were male in their fourth decade and no meaningful association on infection risk could be made with smoking or diabetes as overall numbers remain small. Although every effort towards standardisation of acute treatment of open fractures is made, time to definitive fixation remains variable and is often determined by the soft tissues as well as the overall case complexity of treating polytrauma patients in need of ancillary care. In our study, the mean time from trauma to primary fracture fixation with ETN PROtect™ was 9 days.

We used ETN PROtect™ for primary fracture fixation in 67.9% of cases and in the complex revision scenario in 37.1%. In our primary fixation cohort, we had 3 (7.9%) cases of aseptic non-union but it is important to note that one had a segmental fracture, the other had 5 cm of bone loss and one patient had a history of drug/alcohol abuse. These are known risk factors for non-union and all cases required subsequent surgical intervention to achieve union [18]. We identified one (1.8%) case of infected non-union following primary fixation of a GA type 1 fracture in an obese patient. Microbiology samples identified staph aureus and definitive treatment involved nail removal, debridement, intra-focal antibiotics and application of a circular frame.

Our outcomes following primary fracture fixation are favourable when compared to the multicentre prospective SPRINT trial despite a higher proportion of GAIII fractures in our study, which may represent advances in open fracture treatment over the past 15 years [19]. The SPRINT study reported non-union rates of 8.6% and 4.2% of patients needed a reoperation for infection related causes. Our deep infection rate of 1.8% following ETN PROtect™ in primary fracture fixation is comparable to recent literature investigating antibiotic-coated nails [20]. This supports the use of ETN PROtect™ in primary fracture fixation in high-risk patients when used alongside good surgical and perioperative management as underlined by BOAST.

Studies investigating the use of ETN PROtect™ in complex revision cases are few in the literature. Even less have evaluated the use of these nails specifically in the context of fracture related infection. In our study, when the nail was used for non-union revision surgery following treated FRI, outcomes were not favourable. All five patients required removal of the nail due to infection relapse and further stabilisation with circular frame despite appropriate initial MDT management with staged debridement and intra-focal antibiotics. Similarly, Walter et al. showed that in a study of 13 patients with open tibia fractures treated with ETN PROtect™, two patients treated for FRI required nail removal after consolidation due to deep infection [10]. Schmidmaier et al. in their multicentre analysis of 23 complex revision cases treated with ETN PROtect™ reported infection in two of their patients – both treated for an infected non-union [21]. Moghaddam et al. showed in 36 patients with tibial non-unions (61.1% with identified organism) treated with ETN PROtect™, 80.6% achieved consolidation with three deep infections. The authors concluded that ETN PROtect™ was an effective treatment even in patients with a history of deep infection [22]. A systematic review reports five infection relapses in 38 patients with infected non-unions treated with ETN PROtect™ [23]. In contrast, Metsemakers et al. reported no cases of infection at 18 months in complex revision cases (four FRI non-unions and one aseptic non-union) treated with ETN PROtect™ [24]. Wasko et al. investigated the use of an antibiotic-coated handmade nail for the management of tibial FRI in their study of ten patients with successful resolution of infection in all patients [25]. A study comparing ETN PROtect™ (23 patients) with a regular ETN nail (23 patients) revealed no deep infections in the former group and a single case of osteomyelitis in the latter [26]. All non-FRI cases in our complex revision surgery cohort achieved union and interestingly, we found no significant difference in time to union between primary fracture fixation and complex revision cases. There is no evidence to suggest that local gentamicin elusion has any detrimental effect on fracture healing.

Possible explanations for our 100% relapse rate in the FRI group include patient, surgical or implant factors. Undiagnosed co-morbidities, inadequate debridement and duration/concentration of local antibiotic elution could play a part. Almost 80 per cent of gentamicin in the nail is released in the first 48 h [27]. Antibiotic resistance in patients who have had multiple courses of antibiotic therapy at other institutions should be considered although resistance to local high-dose gentamicin would be unusual. Interestingly, the 2012

ETN PROtect™ brochure stated that the nail should especially be used in the treatment of revision infection cases, however, this was no longer in the 2022 instructions for use.

Further direction of study could include investigating the use of antibiotic-coated nails in association with the Reamer Irrigator Aspirator system (DePuy Synthes) in both septic and aseptic non-unions. Vicenti and colleagues included 17 patients with aseptic non-unions who all achieved bone consolidation at a mean of 7.18 months concluding that ETN PROtect™ nailing in conjunction with the RIA system offers a safe and effective treatment [28]. Our study has Limitations inherent with retrospective case-series. Longer follow-up, patient-related outcome scores and a control group are all potential areas of improvement. Despite being the largest single-centre study in the literature, overall numbers remain small to draw any strong conclusions.

Conclusion

To our knowledge this is the largest single-centre series reporting on the use of antibiotic-coated tibial nails. Based on our experience, we believe that in selected cases, namely high infection risk primary fracture fixation, revision surgery for aseptic non-union and intramedullary nailing following external fixation, the potential reduction in infection rates will offset their high cost. Despite promising results reported in recent literature, we urge caution with their use in previously established infection cases, even in the absence of active infection.

Declarations

Conflict of interest All authors declare we have no conflicts of interest and no funds/grants were received for this study.

Informed consent Informed consent was not required as no patients were contacted for this study and all data were anonymised. The study was registered with the hospital's research department.

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