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ORIGINAL ARTICLE

Prospective Study of Custom-made Cemented Antibiotic Nail for the Treatment of Infected Non-union Tibia Fracture

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Abstract

Background and Objectives: Infection in long bones continues to present a significant challenge because of the necessity for multiple surgeries, extended treatment periods, and an unpredictable prognosis. An antibiotic cement-coated nail has shown promising potential due to the local antibiotic elution as well as the stabilization of bone defects. We conducted this study to compile our insights gained with the use of custom-made antibiotic cement nails for the management of infected as well as non-union tibia fractures. **Methods:** A prospective study was conducted in Rome University Hospital, Italy by enrolling 52 patients who were diagnosed with infected nonunion of the tibia and were treated with custom-made antibiotic-cement-coated nails. A custom-designed cement-coated nail was used for surgical procedures by combining PMMA bone cement, gentamycin PMMA, vancomycin, and sterile mineral oil. The evaluation of functional outcomes was performed in relation to the treatment of infection and the healing of bones. **Results:** After a period of 4 to 6 weeks, it was observed that all infection markers had returned to normal levels and only 7 patients required flap closure and bone graft. A majority of the patients (98%) showed signs of bone healing on x-ray, and there were no indications of infection based on the negative results of infection markers. This positive outcome was observed throughout an average follow-up period of 18 months. **Conclusion:** We found that using a cemented nail impregnated with antibiotics is an effective approach for managing postoperative infections and achieving successful reunion of bone.

Keywords: Infection; Non-Union Tibia; Impregnated Antibiotics; Bone Cement

Introduction

Infected nonunion of long bones is a chronic and debilitating disease with complex pathology. It requires long-term treatment and has an unpredictable outcome, making it challenging for surgeons to manage efficiently in terms of cost and time [1]. Infected nonunion has been defined as a state of failure of union and persistence of infection at the fracture site for 6 to 8 months. There are several contributing factors to the development of infected non-unions, such as open fractures, tissue or bone loss, postoperative infections following internal fixation, chronic osteomyelitis leading to pathologic fractures, and surgical removal of infected bone [2]. One particularly difficult aspect is dealing with infected bone defects following internal fixation. This is because internal fixation can promote the formation of bacterial biofilms, making treatment more difficult [3–5]. The majority of infections related to orthopaedic trauma are caused by bacteria that can form biofilms [6]. A biofilm is comprised of a hydrated matrix composed of polysaccharides and proteins. Once established, it acts as a protective shield for microorganisms, rendering them less susceptible to antimicrobial agents, opsonization, and phagocytosis, thereby playing a significant role in the persistence of infections [7]. Cierny and Mader have proposed four principles to address the issue of bacteria that form biofilms. These principles are based on a thorough examination of surgical debridement, fracture stabilization, soft tissue coverage, and analysis of antibiotic levels to effectively eliminate infection [8]. Following these principles is important in the clinical evaluation and treatment of biofilm infections [9]. Recently, infected non-union tibia cases have been treated using a two-step procedure. The first step involves debridement treatment, where non-antibiotic or antibiotic cemented coated nailing is inserted into a sterile nonunion. The second step involves the restoration of bone stability through internal or external fixations by orthopaedic specialists. However, this approach has undergone a transformation with the advent of antibiotic permeate cement-coated nails. These cement nails soaked in antibiotics have gained attention for their high success rate in stabilizing femur fractures and infected tibia fractures that have not healed properly [5]. Studies have shown that using these antibiotic nails for 36 weeks at the site of infection reduces the incidence of side effects from the infection. These cost-effective antibiotic nails have revolutionized the traditional two-step long-term procedures by allowing for a single-stage approach, which increases the likelihood of early mobilization and eliminates the occurrence of infections at the pin sites. Cement coating of orthopaedic implants is supportive and sometimes necessary in various clinical settings [10–12]. Previous studies have documented the use of antibiotic cement-coated internal fixation for managing infected bone defects in long bones [3,4,13,14]. The retrospective analysis of potential antibiotic regimens by Baerti et al. indicates that meropenem + vancomycin was the most effective empiric treatment in 95.7% of patients with confirmed susceptibility. Meropenem + vancomycin, gentamicin + vancomycin, and co-amoxiclav + glycopeptide are the best therapeutic options for FRI, regardless of the onset of infection. To avoid multidrug resistance, established antibiotic combinations such as co-amoxiclav with a glycopeptide seem to be reasonable as a systemic antibiotic therapy, while vancomycin + gentamicin could be implemented in local antibiotic therapy to reduce adverse events during treatment [15]. In our study, we employed a combination of gentamicin and vancomycin due to their complementary properties that are well-suited for our purpose. The primary objective of our study was to assess the results achieved through the utilization of custom-made antibiotic cement-coated nailing for the treatment of infected nonunion tibia, focusing on its effectiveness in controlling infections and promoting bone union.

Methodology

This prospective study was conducted in Rome University Hospital, Italy over the course of four years, from 2018 to 2022 involving 52 patients aged between 19 to 59 years, who presented with infected non-union tibia and were treated using antibiotic cement-coated nailing. We included patients who had diaphyseal unhealed fractures of the tibia with bone gaps measuring less than 2 cm and excluded those who were allergic to gentamycin or vancomycin. Out of the 52 patients, 36 had open fractures classified as Gustilo Anderson types I (6 patients), II (7 patients), IIIA (9 patients), and IIIB (14 patients), while the remaining 16 had closed fractures. Following a comprehensive preoperative assessment, surgery was performed after obtaining informed consent. Patients with open fractures were primarily managed with wound debridement, intravenous antibiotics, and intramedullary tibia nail fixation, whereas patients with closed fractures received intramedullary tibia nail fixation with prophylactic antibiotic coverage only. Post operatively, tissue samples were collected from 23 patients who developed draining sinuses for further evaluation. The results of tissue samples indicated the presence of *Staphylococcus aureus* in all cases. Additionally, in all patients, preoperative investigations of complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) revealed elevated levels.

Operative procedure

In cases where prior surgery has been performed, the first step involves removing the implant. After that, a thorough debridement of the infected bone as well as soft tissues was carried out with copious lavage. Samples of the bone, soft tissues, as well as any purulent material were collected and forwarded for culture and sensitivity testing. Following debridement and specimen collection, the intramedullary canal was properly reamed and prepared to accommodate a larger diameter nail, and it was meticulously rinsed with saline. Subsequently, the surgical team changed their gowns and gloves as part of aseptic precautions. The limb was re-prepared and re-draped, and an antibiotic-impregnated nail of suitable size was readied on a separate sterile table. Custom-made cemented nail used for the procedure was made using a Nancy nail with a diameter of 4mm, combined with 80 gms of gentamycin PMMA (Polymethyl methacrylate), 2 gms of vancomycin, sterile mineral oil and a chest tube with an inner diameter matching the outer diameter of the last reamer[5]. Few patients were treated with an interlocking nail coated with antibiotic-impregnated PMMA, which combines local antibiotic delivery with stable internal fixation. The length of the nail was determined based on the medullary canal, and a chest tube of similar size to the nail was selected. The chest tube was then cut to match the measured length of the medullary canal, pre-treated with mineral oil, and the elastic nail was cut 5mm longer than the measurement. Additionally, the proximal portion of the nail was bent into a loop. The bone cement was prepared and injected into the lumen of the chest tube. Once the cement started to harden, the Nancy nail was inserted into the chest tube. A surgical knife was used to cut the chest tube longitudinally, and it was carefully peeled away from the cemented nail once the cement had fully hardened into the desired shape. Further, waited till the nail-cement composite to cool down and for the monomer to evaporate. It was important to avoid peeling the chest tube too quickly to prevent the uncured cement from separating from the nail and sticking to the plastic. After the cement nail has completely hardened and cooled at room temperature, which typically occurs within 15 to 20 minutes, the cleaned and hardened nail is placed into the medullary canal of the proximal tibia. The nail loop is left sticking out from the canal, as shown in Fig 1.

The wound was closed, and if deemed necessary, local soft tissue rotational flaps were surgically created. In the postoperative period, the wound was regularly examined at intervals of 48 to 72 hours. Initially, a complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels were assessed. Subsequently, these inflammatory markers were monitored at weekly intervals to track the trends. All patients had their limbs immobilized with splints or casts for a minimum of 6 weeks after the surgery to limit movement at the fracture sites and promote proper osseous healing. Intravenous antibiotics were administered based on the culture sensitivity report, and weekly assessments of infection markers were conducted. Following a period of 6 weeks, the custom-made antibiotic nail was removed, and it was replaced with a definitive tibia nail. After patients were discharged, a follow-up schedule was established. This included appointments every 2 weeks during the first 2 months, followed by monthly visits for the subsequent 6 months, and then every 2 months until the final follow-up was conducted. The average follow-up duration was 25 months. During this time, patients were carefully monitored for indications of wound healing, and fluctuations in blood inflammatory markers, and underwent radiological assessments to evaluate the progress of bone union.

Results

In all 52 cases, the intraoperative specimens revealed positive cultures. Out of these, 37 samples showed positivity for *Staphylococcus aureus*, 11 samples showed positivity for multiple bacteria, and 4 samples showed positivity for *Klebsiella*.

Table 1. Isolated organism from an intraoperative specimen

Patients	Bacteria from specimen
37	*Staphylococcus aureus*
11	Multiple Bacteria
4	*Klebsiella*

Following a period of 4 to 6 weeks, all infection markers returned to normal levels and complete wound healing was observed. Out of the patient cohort, only seven individuals required flap coverage and bone grafting. In 51 patients, which accounts for 98% of the total, follow-up x-rays revealed successful bone healing within an average duration of 18 months. However, one patient, who had undergone surgery 6 months prior, exhibited elevated inflammatory markers and no radiological evidence of bone union. This patient had suffered a high-energy trauma with an open Grade III B fracture, which also resulted in soft tissue loss due to the trauma. The initial treatment for the open fracture involved debridement, lavage, antibiotics administration, and the use of external fixators to stabilize the fracture temporarily. The patient eventually needed a free flap procedure to cover the tibia during a later stage. This patient was readmitted for the purpose of removing the nail and undergoing a two-stage revision. The tissue sample taken from the wound and the medullary canal showed the presence of *Staphylococcus aureus*. After the second stage revision, a final evaluation conducted 12 months later revealed that the fracture had healed both clinically and radiologically, with no signs of recurring infection. The remaining patients, on average, achieved bone union at 18 months, and infection control was typically attained within a duration of 4 to 6 weeks. (Fig 1a, 1b, 1c, 1d and 1e)

Discussion

The study demonstrates the infected nonunion tibia can be effectively treated if the protocol of debridement is correctly followed. The bone stability can be regained within 22 to 48 weeks. Antibiotic-impregnated cemented nail is an ideal

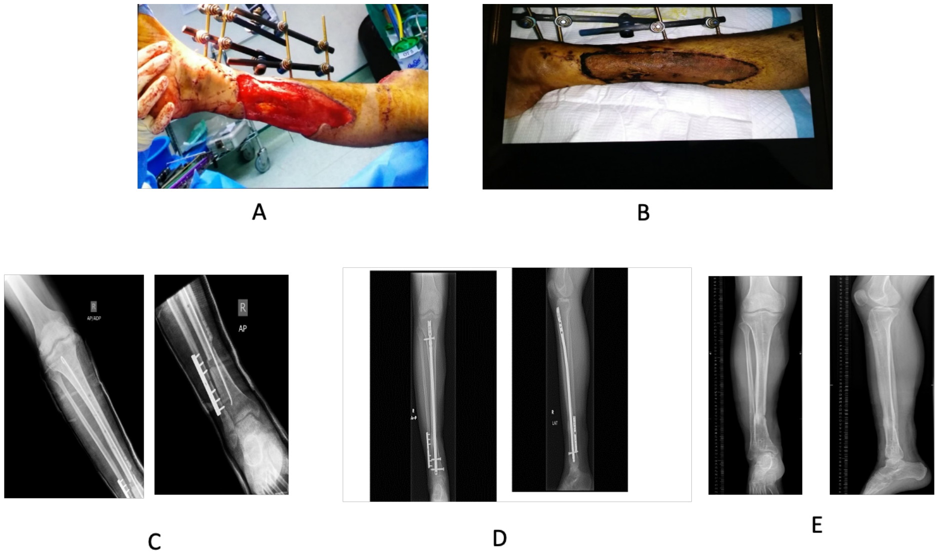

Fig 1. A. Temporary external fixation was fixed to treatsoft tissue, B. Healed soft tissue coverage, C. Post-operative X-rays with custom-made antibiotic-cemented nail, D. After 12 months healed fracture, E. X-rays post Implant removal after 16 months

procedure to control the postoperative infection and achieve reunion. With the development of bacterial biofilms, the need for prolonged treatment, and the uncertainty of the outcome, orthopaedic physicians and their patients are facing a significant challenge when it comes to infected bone defects due to bacterial resistance to drugs[16]. There is currently no universally accepted set of guidelines for managing these types of defects. The conventional approach to managing infected bone defects has involved a multi-stage procedure. This procedure begins with controlling the infection and is followed by reconstructing the bone defect using internal fixation and bone grafting, often with the use of external fixation or antibiotic-impregnated cement beads. While the traditional procedure has demonstrated its effectiveness, it has also exhibited certain disadvantages. Firstly, it requires multiple operation stages and secondly, the utilization of external fixation is linked to a relatively elevated occurrence of infections at the pin sites. In certain instances, the use of external fixation involving a pin can lead to the piercing of soft tissues, resulting in muscle contracture and restricted movement in the joint, especially in the femur fractures[17]. Furthermore, certain patients who are obese exhibit inadequate adherence to external fixation procedures, including pin site care. Thirdly, antibiotic-impregnated PMMA cement beads have traditionally been employed to administer antibiotics directly to the site of infection. Nevertheless, this method fails to ensure sustained efficacy for the affected area[18]. One effective method to reduce infection rates is to carefully time the initial internal fixation procedure,[18]. Timely disinfection and removal of dead tissue are essential for the successful treatment of open wounds caused by war trauma. Proper management of these wounds is critical for a positive outcome. The optimal time for wound treatment is within two hours of the injury. Hence, timely wound treatment can prevent contaminated wounds from progressing into infected wounds, which is of utmost importance in the management of acute open wounds. The same approach is taken when treating patients with open fractures in order to perform early debridement. For individuals with open fractures and soft tissue defects resulting from firearm injuries, the application of corticospongioplastics after completing phase I debridement of wounds smaller than 4 cm has shown positive results. For wounds larger than 4 cm, the Lizarov method has proven advantageous[19,20]. In addition, the Ilizarov technique offers a practical solution for treating open bone defects caused by firearm injuries, with a relatively short surgery time. When dealing with chronic osteomyelitis, controlling the infection is of utmost importance. Once the infection is under control, various methods can be used to repair and reconstruct the bone defects. The Ilizarov method is also a suitable choice for patients who have insufficient soft tissue conditions and are not suitable candidates for flap repair. In appropriate cases, corticospongioplastics should be considered. There is a wide range of literature available that highlights the benefits of using antibiotic-loaded cemented nails in managing infections and achieving bone union through a single-step procedure[14,21]. This involves using antibiotic bone cement-coated internal fixation during the initial stage[22]. By using the antibiotic bone cement-coated nail, both infection and stability concerns can be tackled concurrently. It is well-established that intramedullary infections tend to spread throughout the entire canal. Therefore, it is more efficient and versatile to eliminate the dead space through intramedullary contact[21]. Furthermore, the antibiotic released locally from the cement-coated nail may exert a bactericidal effect on bacterial biofilms. Additionally, the intramedullary nail can offer a relatively sturdy fixation and stability at the defect site, which can be advantageous for both infection management and bone union[22–24].

In this research, we utilized vancomycin and gentamicin as antibiotics loaded onto the bone cement. Osteomyelitis usually occurs as a result of various microorganisms, with *Staphylococcus aureus* being the most commonly reported bacteria in medical literature[25]. In about 65% to 70% of cases, *Staphylococcus aureus* is found alongside other pathogenic bacteria. Local antibiotics like Gentamicin, Tobramycin, Meropenem, and Vancomycin are frequently used due to their wide range of antibacterial activity, stability at high temperatures, and low sensitivity to resistance[26]. In earlier studies, vancomycin, and gentamicin, or sometimes tobramycin, were more commonly chosen as antibiotic agents[8,14,27]. In our study, *Staphylococcus aureus* was identified in 37 out of 52 cases, multiple bacteria in 11 out of 52 cases, and *Klebsiella* in 4 out of 52 cases. The choice of local antibiotic was primarily based on the results of bacterial culture and drug sensitivity. The increasing drug resistance patterns indicate that profound pathogenic bacteria, including intramedullary infection, exhibit resistance to gentamicin[28]. The current duration of treatment for bone infections is typically over six weeks. However, there is ongoing discussion about whether to administer the treatment intravenously or orally. Some studies suggest that oral antibiotics are just as effective as intravenous antibiotics during the first six weeks of infection. Additionally, using oral antibiotics can shorten hospital stays and reduce the risk of cross-infection while in the hospital[29]. It is important to refer to the bacterial culture results and the advice of clinical pharmacists to determine the appropriate duration of intravenous antibiotics. In our study, intravenous antibiotics were administered for a period of six weeks. Notably, infection in all cases was effectively managed in a single phase, underscoring the benefits of utilizing personalized intramedullary nails in controlling infections. Paley and Herzenberg have also recorded successful infection control in nine cases[27]. Thonse and Conway have reported a rate of 85% for infection control in their study[5].

Jokhia and their colleagues found that bone union occurred in 80% of cases without requiring any additional procedures[30], Bhatia and their team reported a 95% success rate in eliminating the infection.[11] Comparable findings have demonstrated that the bone cement nail exhibits a satisfactory effect in controlling infections[31]. Varying outcomes have been observed across different studies with respect to bone union. Bhatia et al. documented a 60% rate of bone union without the need for supplementary procedures[11]. Zheng and Hang have reported a union rate of 22%[32]. Thonse and Conway have reported a union rate of 73%[5]. In our study, 51 cases (98%) exhibited direct healing in the initial stage, with an average duration of 18 months. It is noteworthy that Shyam et al. have previously reported cases that underwent successful healing in the first stage, provided that the bone defect range was less than 4 cm[33]. Owing to the limited number of cases, it is hard to correlate the association between the magnitude of bone defect and the primary healing effect. In our study, we initiated weight bearing partially at postoperative 8 weeks and allowed full weight bearing as tolerated with crutches at 3 months. One patient required readmission for the purpose of nail removal and two-stage revision. Recent research indicates that the combination of teriparatide and the Ilizarov technique in the management of hematogenous osteomyelitis can accelerate the mineralization pace of fresh bone post-bone removal, thereby facilitating the prompt elimination of the external frame[34]. Teriparatide is a pharmaceutical agent that facilitates bone formation. It represents a viable approach to expedite bone healing when employed in conjunction with surgical intervention, thereby enhancing the efficacy of the procedure and yielding favourable outcomes. However, most patients currently receiving treatment have limited financial resources. The use of teriparatide further worsens the financial burden on these individuals, which is an important issue that needs to be addressed.

At present, PMMA is commonly employed for the purpose of nail coating. However, PMMA is non-biodegradable and its surgical removal can pose challenges. The major problematic consequence after non-union is nail breakage. Previous removal techniques have been described with satisfactory outcomes[35,36]. Timely removal of nails is recommended once the infection has subsided because theoretically live bacteria are known to persist on antibiotic-impregnated cement under *in vitro* conditions. Furthermore, concerns persist regarding its thermal reaction, antibiotic release profile, as well as toxicity effects. Anugraha et al. have conducted research on the utilization of a biocomposite consisting of calcium sulphate and hydroxyapatite as a coating for nails. This innovative approach offers promising new possibilities[27]. Our study had certain limitations, firstly, it was a prospective study with a relatively small sample size. Secondly, the bone infection site was not localized but rather dispersed. It is important to note that the application of mineral oil on the nail surface could potentially lead to localized inflammatory reactions. Lastly, additional research is required to gain a comprehensive understanding of the biomechanics involved in the use of intramedullary nail bone cement.

Conclusion

The custom-made antibiotic cement-coated intramedullary nail employed in this study demonstrates superior filling properties and represents an ideal approach for postoperative infection control and the successful union of long bones. It boasts a high rate of infection control, with some cases achieving direct bone healing. In contrast to external fixation, it eliminates the need for a complex external fixation frame assembly and is well-received by patients. Moreover, it is a cost-effective option and is particularly suitable for resource-constrained and developing countries where managing infected nonunion of long bones poses significant challenges.

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