Management of Infected Tibial Nonunion: Combining Synthetic Bone Grafting with Continuous Local Antibiotic Perfusion (CLAP)

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Financial support: The corresponding author (A.M.) received consultant fees to develop the CLAP system from Cubex Medical. The remaining authors have no conflicts of interest to declare

Conflict of interest: None declared

Patient: Female, 31-year-old
Final Diagnosis: Infected nonunion
Symptoms: Infection • nonunion
Clinical Procedure: —
Specialty: Orthopedics and Traumatology

Objective: Unusual or unexpected effect of treatment

Background: Infection control and reconstruction of bone and soft tissue are essential for treating infected nonunion. Continuous local antibiotic perfusion (CLAP) is a drug delivery system that continuously delivers antibiotics at the required concentration, area, and duration. This case report describes the instance of infected nonunion in which infection eradication and bone union were achieved using CLAP and synthetic bone grafting while retaining the implant.

Case Report: The case was a 31-year-old woman with an infected nonunion. After she underwent osteosynthesis using nail for open fractures of tibia and fibula, bone union remained unachieved, and she exhibited skin defects and draining of pus. Following the removal of the infected granulation tissue from the bone defects, 2 bone marrow needles, serving as intramedullary antibiotic perfusion (iMAP) pins, were inserted into the medullary cavity tibia. A double-lumen tube was placed in the subcutaneous pocket as the intra-soft tissue antibiotic perfusion (iSAP) tube. No bone mobility was observed around the bone defect and nail, and replacement of the implant was not necessary. Beta-tricalcium phosphate was transplanted to the bone defect, and negative pressure wound therapy was applied. Gentamicin was injected continuously through iMAP and iSAP. Finally, the infection was eradicated, and cortical bone bridging was observed without additional surgery or adverse effects.

Conclusions: CLAP emerges as a viable treatment option for infected nonunion, as it enables the delivery of antibiotics at a concentration sufficient for infection control while providing the surgeon with flexibility to design the area, dosage, and duration of antibiotic delivery.

Keywords: Bone Diseases, Infectious • Bone Regeneration • Drug Delivery Systems • Gentamicins • beta-Tricalcium Phosphate

Abbreviations: β-TCP – beta-tricalcium phosphate; CLAP – continuous local antibiotic perfusion; iMAP – intramedullary antibiotic perfusion; iSAP – intra-soft tissue antibiotic perfusion

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/945023

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Introduction

The treatment of an infected nonunion requires infection control and the reconstruction of bone and soft tissue. Despite advancements in treatment methods, infected nonunions persist as difficult-to-treat orthopedic problems. Generally, standard treatment involves complete resection around the infected lesion, followed by soft tissue and skeletal reconstruction [1]. This requires multiple surgical procedures and an extended treatment duration, imposing a heavy burden on patients [2].

We recently introduced a case series in which fracture-related infections were treated with continuous local antibiotic perfusion (CLAP) [3,4]. CLAP is an antibiotic delivery system consisting of intramedullary antibiotic perfusion (iMAP) and intra-soft tissue antibiotic perfusion (iSAP), which continuously delivers antibiotics at the required concentration, area, and duration, with negative pressure assistance. This system facilitates infection control while retaining the implants and tissues affected by the bacteria. In this report, we describe the case of an infected nonunion in which infection eradication and bone union were achieved using CLAP and synthetic bone grafting, while retaining the implant. Retaining the nail prevents the infection from spreading to healthy tissue, including the knee joint. Since this technique does not require autologous bone grafting, it is much less invasive than standard treatments.

Case Report

The patient, a 31-year-old woman, presented with a medical history of eating disorders and depression and had been taking aripiprazole, nitrazepam, topiramate, clonazepam, and sodium valproate. She had no history of alcohol intake or smoking. At the age of 29 years, she sustained injuries to her left tibia and fibula, resulting in open fractures classified as Gustilo-Anderson type IIIA (Figure 1A). Within 3 h of the injury, she underwent debridement and osteosynthesis using an intramedullary nail (Figure 1B). Subsequently, she began walking with a patellar tendon-bearing brace and was discharged without signs of infection. However, she continued to experience walking pain 12 months after surgery. At 15 months after injury, she exhibited skin defects and pus drainage near the wound without bone union (Figure 2A, 2B). The infection was not controlled.
Figure 2. (A) Photographs 15 months after osteosynthesis using an intramedullary nail. The patient began exhibiting skin defects and draining of pus proximal to the wound. (B) Radiographs and computed tomography scans 27 months after the first surgery. The fracture was not united, and bone defects were observed at the anterior and medial parts of the fracture site.
even after several weeks of intravenous antibiotic treatment. Following a period of treatment interruption owing to mental issues, the 2 screws around the skin defect were removed 21 months after surgery; however, the symptoms persisted. At 27 months after surgery, the patient consented to surgical intervention to address the infected nonunion.

Under general anesthesia, a Z-shaped skin incision was made around the fistula, extending 4 cm both proximally and distally on the medial side of the left lower leg. The fistula communicated with the bone defect through the subcutaneous pocket, with pus and infectious tissue filling the bone defect (Figure 3A). The bone defects measured 2.5×1 cm, mainly in the anterior and medial aspects of the distal tibia (Figure 3B). Despite the removal of the distal screws, no bone mobility was observed around the bone defect and nail. After assessing the nonunion stability, we concluded that implant exchange or additional plate fixation to improve fixation was not necessary. We also determined to retain the nail because there was a risk that the infection, which was thought to be localized in the distal tibia, might spread to healthy tissue, including the knee joint, by removing the nail.

Figure 3. Photographs taken during surgery. (A) The fistula communicated with the bone defect through the subcutaneous pocket, with pus and infectious tissue filling the bone defect. (B) The bone defect measured 2.5×1 cm, mainly in the anterior and medial aspects of the distal tibia.
Following the removal of the infected granulation tissue from the bone defects, 2 bone marrow needles (Senko Medical, Tokyo, Japan) with a diameter of 3 mm, serving as iMAP pins, were inserted percutaneously into the medullary cavity of the proximal and distal tibia. Sclerotic changes were observed on the surface of the bone defect, prompting the creation of multiple drill holes using a 1.0 mm Kirschner wire to intersect the normal medullary canal and infected region. A 22 Fr double-lumen tube (Salem sump tube; Covidien, Japan) was placed in the subcutaneous pocket as an iSAP tube. Upon injection of saline through the iMAP pins, the contaminated yellow tissue containing pus flowed out of the medullary canal. This irrigation continued until the discharge became clear. Beta-tricalcium phosphate ($\beta$-TCP) was transplanted to the bone defect. Following skin closure, a 1×1-cm skin defect remained, and negative-pressure wound therapy was applied over the subcutaneous pocket and skin defect. Fluid infused through the iMAP pins and iSAP tubes was aspirated through the negative-pressure wound therapy and iSAP tubes, confirming fluid perfusion throughout the infected area (Figure 4A, 4B).

Gentamicin was injected continuously at a concentration of 1200 µg/mL at a rate of 2.0 mL/h via iMAP pins and iSAP tubes immediately after surgery. Six days postoperatively, the serum concentration of gentamicin was above 2.0 µg/mL, prompting a reduction in injection concentration to 600 µg/mL. Subsequently, serum concentrations remained below 1.0 µg/mL. The effluent concentrations of gentamicin measured at 2 and 6 days postoperatively were 680 µg/mL and 780 µg/mL, respectively. All the pins and tubes were removed on postoperative day 20.

The skin defects gradually reduced as swelling decreased, finally healing without additional surgery 1 month after the procedure (Figure 5). The patient regained the ability to walk without weight-bearing limitations. Tissue cultures revealed the presence of 2 microorganisms: Streptococcus agalactiae and Citrobacter freundii, which are resistant to gentamicin. Intravenous antibacterial treatment with 6.0 g/day of ampicillin/sulbactam was administered until 1 month postoperatively, followed by a switch to oral antibiotics, which continued until 3 months postoperatively. C-reactive protein levels
Figure 5. Photographs of skin-defect area. Negative pressure wound therapy was applied over the subcutaneous pocket and skin defect. Skin defects gradually reduced as swelling decreased, finally healing without additional surgery 1 month after the continuous local antibiotic perfusion surgery.

Figure 6. Graph of blood test data and locally/intravenously administered antibiotics. WBC – white blood cells; CRP – C-reactive protein; conc – concentration; GM – gentamicin; ABPC/SBT – ampicillin/sulbactam.
normalized 9 days postoperatively and remained within the reference range thereafter (Figure 6). No adverse effects were observed during these treatments, and the patient was discharged 46 days after surgery, without the need for additional surgery. Unexpectedly, bone remodeling progressed at the β-TCP transplant site, and cortical bone bridging and new bone formation in the medullary cavity were observed 15 months after continuous local antibiotic perfusion surgery. (Figure 7A, 7B). Nail removal was performed 3 years after surgery, and the patient had not experienced a recurrence of infection at 3.5 years after surgery. The patient was able to walk with a patellar tendon-bearing brace before nonunion surgery, walk with a cane 1 month after surgery, and walk unassisted at the final follow-up, with visual analog scale scores of 4, 2, and 0, respectively.

Discussion

Advantages of CLAP

This is the report of an infected nonunion that was treated by retaining the implant and performing one-stage synthetic bone grafting for the bone defect in combination with CLAP. The advantage of CLAP lies in its ability to deliver a high concentration of gentamicin, which can destroy biofilms, even those formed by drug-resistant microbes. In the present case, implants believed to be coated with biofilms of gentamicin-resistant microbes developed during long-term infection were successfully retained. In addition, fracture healing was achieved using a synthetic bone graft.

Figure 7. Radiographs of the nonunion site until 15 months after surgery (Above: anteroposterior view, Below: lateral view). Bone remodeling continued to progress at the β-TCP transplant site, and cortical bone bridging and new bone formation in the medullary cavity were observed 15 months after continuous local antibiotic perfusion surgery.
Comparison with Previous CLAP Cases

According to the literature, there are 16 case reports or case series papers related to CLAP, 6 of which are about fracture-related infection. Of these, 2 of the studies included cases in which infection occurred more than 10 weeks after the fracture, and, as in our case, the infection was successfully treated with CLAP, while retaining the implant [4, 5]. In these studies, autologous bone grafting was performed in cases with bone defects, while no cases of healing using synthetic bone grafting were reported. In the present case, we planned additional surgery to exchange or compensate for the bone defect after the synthetic bone graft; however, unexpectedly, bone union was achieved without an additional surgery. Treatment with synthetic bone graft alone might be a good option, without loss of autologous bone.

Comparison with Traditional Methods

One of the standard treatments for infected nonunion is the Masquelet technique [6]. The treatment principle involves the complete removal of tissues with poor vascularity, including sclerotic bone and metal implants. Subsequently, bone cement is placed in the bone defect [7]. This can reduce the risk of re-infection but can also increase the risk of bone instability and re-fracture. Other treatment options include fixation with an antibiotic-coated nail, which has been reported to control infection but presents challenges such as nail breakage and difficulty in removal [8, 9]. In both treatments, the antibiotics eluted from the bone cement remain at high concentrations for the first few days and then rapidly decrease to subtherapeutic levels [10]. After this period, biofilm can form on the cement surface, necessitating surgical removal. In contrast, CLAP allows the administration of high supratherapeutic concentrations of antibiotics for the required duration without increasing the risk of re-fracture or implant fracture and without the need for additional surgery for removal.

Efficacy of Gentamicin in CLAP

Gentamicin is known for its efficacy against bacterial biofilms in postoperative orthopaedic infections, and high concentrations have sufficient antibacterial activity regardless of susceptibility [11]. In the present case, the effluent gentamicin concentrations at 2 and 6 days after surgery were 680 µg/mL and 780 µg/mL, respectively, and were estimated to exceed a minimal inhibitory concentration of gentamicin-resistant microbes.

Retaining Nail

In the present case, we considered that there were many benefits to not exchanging the implant. Since the radiographic images did not show any loosening around the proximal nail, we judged that the infection was localized in the distal tibia. In the exchange of the implant, the existing nail, which was previously inserted antegradely, must have been removed through the knee joint, which could have caused infection to spread to the proximal tibia and knee joint. Treatment using CLAP allowed us to administer antibiotics at local concentrations that could control the biofilm; therefore, we thought there was a chance of eradicating the infection. In addition, we thought the patient would not be able to tolerate prolonged and highly invasive surgery because of her mental health status. Therefore, we chose these less invasive and shorter treatments first. However, if we had failed to control the infection, we might have switched to standard treatments, such as exchanging the nail.

Synthetic Bone Remodeling

One-stage treatment of infected cases with bone defects using antimicrobial-containing calcium sulfate or antimicrobial-impregnated allograft has been reported to result in infection control and subsequent bone formation in the bone defect, contrary to the conventional treatment principle advocating for the removal of material with poor blood flow [12, 13]. In the present case, we used β-TCP, a synthetic bone, as a scaffold. Autologous bone grafting is common for bone defects, and we planned it as the next surgery. However, β-TCP remodeling had already progressed unexpectedly. We inferred that multiple drill holes with Kirschner wires, a standard technique in CLAP to perfuse antibiotics to infected but biologically active areas, allowed us to avoid unnecessary extensive curettage. Additionally, this induced osteogenic cells and growth factors from the normal bone marrow into the β-TCP, which acts as the osteoconductive scaffold, resulting in bone healing.

Future Directions

When treating with CLAP, there is a possibility that antibiotics will not reach the required concentration and area, necessitating careful observation, especially in cases of minimal curettage and implant preservation. The identification of synthetic bone remodeling subsequent to the eradication of the infection was a novel discovery in the present case. However, we considered that complete bone union may not be achieved in all cases using synthetic bone, and such cases require second-stage reconstruction planning. In the future, it will be necessary to investigate this issue with multiple cases.

Conclusions

We encountered a case of a patient with an infected nonunion for which infection control and bone union were achieved without implant replacement or autologous bone grafting, using
CLAP. CLAP emerges as a viable treatment option for infected nonunion, as it enables the delivery of antibiotics at a concentration sufficient for infection control while providing the surgeon with flexibility to design the area, dosage, and duration of antibiotic delivery. An individualized treatment plan is important, as a thorough evaluation of the nonunion stability and the infection area can provide less invasive treatment options.

**Acknowledgements**

We would like to thank Editage (www.editage.jp) for English language editing.

**References:**


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