

Successful treatment of chronic osteomyelitis in children with debridement, antibiotic-laden cement spacer and bone graft substitute

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Received: 18 May 2016 / Accepted: 9 September 2016 / Published online: 19 September 2016
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Abstract

Purpose Chronic osteomyelitis and infected nonunion are relatively rare conditions in pediatric patients and are more frequently seen in developing countries. Although relatively rare, they are medically and surgically challenging. Here we report a novel surgical technique used to manage five patients with chronic osteomyelitis of long bones.

Methods Five skeletally immature patients with chronic osteomyelitis and infected nonunion of the long bones were treated surgically between 2010 and 2014 by a combination of resection of necrotic infected bone, debridement of surrounding soft tissue, and application of antibiotic-laden cement spacer inducing periosteal membrane before final bone reconstruction. Once inflammatory markers normalized, all the patients were re-operated for cement removal, bone graft substitution, and concomitant osteosynthesis of the affected bone, if needed. All patients underwent MRI, CT scan, and laboratory evaluation prior to surgery. The antibiotic regimen was started empirically and then adjusted according to culture and sensitivity results.

Results Mean patient age at the time of diagnosis was 11 years (range 4–14), and all patients had at least 2-year follow-up (range 2–5). At last follow-up, clinical and laboratory evaluation had normalized, the bone had healed, and all patients had resumed daily living and sports activities.

Conclusion Surgical debridement is the standard approach to chronic osteomyelitis. Use of antibiotic-laden cement is

recommended to penetrate local infection, with antibiotic therapy playing an adjunctive role. The cement also induces membrane formation that aids bone reconstruction.

Level of evidence IV.

Keywords Chronic osteomyelitis · Children · Antibiotic · Cement · Induced membrane

Introduction

Though relatively rare in the pediatric age group, chronic osteomyelitis (CO) and infected nonunion are challenging medical and surgical conditions. The long duration of treatment necessitates the cooperation of patients and their families [1–6], and a multidisciplinary approach is naturally required to ensure satisfactory outcomes [2, 3, 6]. The gold standard step in the surgical approach to CO is a sharp debridement of necrotic tissue, abundant lavage, sequestrectomy, and removal of any hardware and/or foreign bodies [5–7]. The use of antibiotic-laden cement (ALC) is recommended to control infection locally, with antibiotic therapy playing an adjunctive role. The cement also induces membrane formation that aids bone reconstruction [5, 8–10]. In particular, the induced membrane technique proposed in 1986 by Masquelet has been shown to be effective in treating bone defects regardless of their magnitude or etiology. The technique can be used in case of initial infection and to control established infection before final bone reconstruction [9–11].

The primary aim of this work was to present a relatively novel surgical approach used to manage five consecutive skeletally immature patients with CO and infected nonunion of the long bones. The patients were treated surgically by a combination of resection of necrotic infected bone, debridement of surrounding soft tissue, and

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application of ALC spacer inducing periosteal membrane before final bone reconstruction. Secondary aims were to evaluate the outcome and efficacy of treatment with the reported surgical technique in children with CO and infected nonunion, and the possible limitations of the procedure.

Materials and methods

Five skeletally immature patients (four males, one female) with CO and infected nonunion of the long bones were retrospectively reviewed after securing institutional review board approval.

The demographic and clinical data recorded were age, gender, etiology of the infection, anatomic location, side involved, details of surgical procedures, causative agent, and length of follow-up (Table 1).

All patients had a clinical examination and laboratory analyses including white blood cells (WBCs), C-reactive protein (CRP), and sedimentation rate (ESR).

All patients had standard anteroposterior (AP) and lateral radiographs of the affected bone, CT scan, MRI, and a bone scan (BS) to confirm the diagnosis of CO or infected nonunion. In particular, CT scan and MRI were performed to evaluate the extent and anatomy of the lesion (Fig. 1).

Surgical technique and follow-up

All patients were treated surgically with a two-step approach. In the first step, the patient was cleared of any hardware and/or foreign bodies, followed by surgical debridement (resection of necrotic and infected bone and surrounding soft tissue), abundant low- and high-pressure lavage, and application of antibiotic-laden cement (ALC). To prepare the ALC, the monomer catalyst (20 mL) was added to methyl methacrylate powder (40.8 g, gentamicin 1 × 0.5 g) and mixed to a 'dough'-like consistency. The cement was shaped to fill the bone defect, and once it began to stiffen it was placed in the bone. The polymethyl methacrylate spacer (Palacos® R + Gentamicin, Heraeus, Wehrheim, Germany) was placed in the defect to produce

Table 1 Patient demographics and clinical data at the onset of chronic osteomyelitis diagnosis

Pt	Age (years) Gender	Mechanism Site Location	Initial treatment	Months after initial surgery	Causative agent Diagnosis	Clinical and laboratory data	Time for normalization of laboratory results	Final treatment (bone substitute ± internal fixation)	FU (years)
1	14 M	Cycling accident Left femur midshaft	ESIN	8 months	<i>Methicillin-sensitive Staphylococcus aureus</i> CO	Pain swelling inflammation WBC < 10 k CRP: 127 ESR: 37	1 month	β-Tricalcium phosphate + rigid nail	5
2	14 M	Motorcycle accident Right femur distal	Plate/screws	18 months	<i>Methicillin-sensitive Staphylococcus aureus</i> CO	Limited ROM WBC: 5.7 k CRP: 37.6 ESR: 64	1 month	β-Tricalcium phosphate	4
3	10 M	Fall Right humerus distal	ESIN	6 months	<i>Methicillin-sensitive Staphylococcus aureus</i> Infected nonunion	Pain swelling fever WBC:<10 k CRP: 90 ESR: 77	3 weeks	β-Tricalcium phosphate + plate/screws	2
4	4 M	Fall Right humerus distal	Kirschner wires	5 months	<i>Cronobacter sakazakii</i> CO	Pain swelling apyretic WBC < 10 k CRP < 2.9	3 weeks	β-Tricalcium phosphate	2
5	13 F	– Left 1st metatarsal	–	–	<i>Methicillin-sensitive Staphylococcus aureus</i> CO	Pain swelling WBC/10.6 k CRP: 37.6	3 weeks	β-Tricalcium phosphate	2

Pt patient, M male, F female, CO chronic osteomyelitis, ROM range of movement, CRP C-reactive protein, ESR erythrocyte sedimentation rate, WBC white blood cells, ESIN elastic stable intramedullary nailing, FU follow-up



Fig. 1 **a** AP and LL X-ray of left femur with infected pseudoarthrosis after osteosynthesis with elastic intramedullary nail; **b** gadolinium injection MRI showing sequestrum and abscess collection;

c postoperative X-ray showing antibiotic-laden cement (ALC); **d** 1-year follow-up X-ray after removal of ALC, substitution with bone graft, and fixation with femoral nail

a bioactive membrane, which is considered as biochemically and physically mature at 4–8 weeks after spacer placement [9, 10]. Also, as elution of antibiotic occurs from the surface of the cement, a K-wire was used to create multiple small pits over the surface [1]. As the antibiotic diffuses within the surrounding hematoma, which acts as a transporter, drain application is not always recommended. The drain could also form an inroad for germs to a poorly vascularized area. Unless the case needs a drain, such as when risk of bleeding is suspected, the drain can be opened every 6–8 h for 15 min to allow periodic drainage of the wound and let the eluted antibiotic act locally before being periodically drained out. Drain removal should be considered as soon as possible once the drainage level decreases [1]. For our series, drainage was applied as and when needed, and the limb was immobilized in a posterior splint (long-arm cast or long-leg cast) in order to protect it from pathological fractures.

Antibiotic therapy was initially started with an intravenous large-spectrum antibiotic immediately after sample collection. After isolation and identification of bacteria, the antibiotic was changed based on the antibiogram spectrum (Table 2).

The ALC spacer was kept in place at least until normalization of infection markers, in particular WBCs and CRP, and then removed in a secondary intervention. The bone defect was packed with bone substitutes within the induced membrane (β -Tricalcium phosphate), with concomitant osteosynthesis performed as needed. All patients had regular clinical and radiographic follow-up with standard AP and lateral radiographs of the affected bone (Fig. 2).

Results

The study included a total of five patients (four males, one female) with CO (four cases) and infected nonunion (one case; patient 3) of the long bones. Mean patient age at time of diagnosis was 11 years (range 4–14). Side involved was the right in three cases and the left in two cases (Table 1). All patients had at least 2-year follow-up (range 2–5).

Causative pathogen was methicillin-sensitive *Staphylococcus Aureus* in four cases and *Cronobacter Sakazakii* in one case (Table 2).

All patients were treated as per the reported technique. The four patients with CO were surgically treated within

Table 2 Causative agent, antibiotic treatment, follow-up (FU), and final outcome

Patient	Causative agent	Intravenous antibiotics (duration)	Oral antibiotics (duration)	FU (years)	Outcome Complications
1	<i>Methicillin-sensitive Staphylococcus Aureus</i>	Oxacillin + gentamicin 28 days	Levofloxacin + rifamycin 6 months	5	Good –
2	<i>Methicillin-sensitive Staphylococcus Aureus</i>	Fucidin + dalacin 28 days	Fucidin + dalacin 3 months	4	Satisfactory Reduced knee flexion (125° right–135° left)
3	<i>Methicillin-sensitive Staphylococcus Aureus</i>	Oxacillin + gentamicin 21 days	Amoxicillin 3 months	2	Good –
4	<i>Cronobacter Sakazakii</i>	Ceftriaxone 21 days	Sulfamethoxazole– trimethoprim 1.5 months	2	Good –
5	<i>Methicillin-sensitive Staphylococcus Aureus</i>	Oxacillin + gentamicin 21 days	Amoxicillin 3 months	2	Good –



Fig. 2 **a** AP and LL X-ray of right femur with chronic osteomyelitis; **b** frontal and axial T1-weight MRI after hardware removal and position of antibiotic-laden cement (ALC); **c** AP and LL X-ray

showing ALC; **d** 2-year follow-up AP and LL X-ray showing bone remodeling after removal of ALC and substitution with bone graft

5–18 months from time of initial surgical procedure (Table 1). The bone defect was filled with β -Tricalcium phosphate bone substitute in all cases. Additional internal fixation with a rigid nail (patient 1) or plate and screws (patient 3) was performed in two patients. No cases of pathological fractures were observed (Table 1).

Clinical and laboratory data, antibiotic treatment, causative agent, and length of follow-up are reported in Tables 1 and 2.

Once the inflammatory markers were normalized, intravenous antibiotics were switched to oral regimen according to bacterial sensitivity (Table 2). Mean duration



Fig. 3 **a** AP and LL X-ray of right humerus with infected pseudoarthrosis; **b** postoperative X-ray after removal of antibiotic-laden cement (ALC), substitution with bone graft, and internal

fixation with plate and screws; **c** 1-year follow-up AP and lateral X-ray views showing bone healing

of intravenous antibiotics was 24 days (range 21–28). Mean duration of oral antibiotics was 3.3 months (range 1.5–6).

At last follow-up visit, all patients had resumed daily living and sports activities, inflammatory markers remained within the normal range, and none of the patients showed signs of growth arrest or disturbances based on radiological and clinical assessment. All patients were pain-free at last follow-up, and range of motion of the affected extremity was comparable to the non-operated side in all patients but one (patient 2). The patient, at the 4-year last follow-up, had resumed daily activities and sports, although his right knee showed a relatively limited flexion of 125° compared to 135° on the contralateral side (Fig. 3).

Discussion

CO and infected nonunion in skeletally immature patients are reported to cause several complications and morbidity [4–7], with documented cases of growth disturbance and limb discrepancy, bone and/or soft tissue loss, and amputations [9, 12–15]. Definitive management of CO and infected nonunion requires aggressive surgical debridement and reconstruction followed by antibiotic therapy [3, 6, 7].

All of our patients with CO and infected nonunion were surgically treated by a combination of resection of necrotic infected bone, debridement of surrounding soft tissue, and application of ALC spacer followed by placement of β -tricalcium phosphate bone substitute into the induced membrane (Tables 1, 2).

The technique pioneered by Masquelet involves initial wide debridement and the placement of a spacer to temporarily fill the bony defect [10]. This step is followed—about 4–8 weeks later—by removal of the spacer and

placement of bone graft into the induced membrane [9–11, 16]. The membrane is primarily composed of type I collagen, fibroblasts, and blood vessels (inner surface), and it secretes bone morphogenetic protein 2, vascular endothelial growth factor, core-binding factor α 1, interleukin-6, collagenase-1, and other growth factors to stimulate bone defect reconstruction. The technique has been shown to promote consolidation of cancellous bone graft within an induced membrane in segmental bone defects of up to 20–25 cm in length [9–11, 16–22].

Few studies have assessed the outcome of adult patients with diaphyseal septic bone loss managed with the induced membrane technique.

Woon et al. (2 patients) [17], Scholz et al. (13 patients) [18], and Wang et al. (32 patients) [19] reported satisfactory clinical and radiological outcome. The mean radiographic time to bone union was between 4 and 6 months, regardless of the length of the bone defect. All authors concluded the Masquelet technique can be used successfully to manage diaphyseal septic bone loss in adults. However, they all stress out the technique must be combined with stable fixation, as instability may lead to deformity or nonunion [17–19].

More recently, Xie et al. [20] reported the early effects of induced membrane technique for the reconstruction of large CO defects in limbs of 23 adult patients. Authors concluded the combination of through debridement with induced membrane technique provides satisfactory clinical outcome and, most importantly, shortens the length of treatment and lowers the rate of complications [20].

On the other hand, Marias and Ferreira (7 patients) [21] and Spigel et al. (25 patients) [22] have managed large septic (CO) bone defects with bone transport through an induced membrane. However, despite the high consolidation rate (97 % overall), the number of complications was high. The authors pointed out that the high morbidity may

be related to the complexity of the surgical procedure and the severity of cases [21, 22].

The induced membrane technique has shown to be a viable option for the treatment of segmental bony defects but has not been specifically studied in the treatment of CO and infected nonunion in skeletally immature patients [5, 8–11, 16–22].

In our group of skeletally immature patients, the induced periosteal membrane was already formed when the ALC spacer was removed (at an average 4 weeks from initial

debridement) and inflammatory markers had normalized. This finding suggests children may be able to generate a periosteal membrane faster than adults. The membrane appeared to prevent graft resorption and promote revascularization and consolidation of new bone. Moreover, the thickened periosteum, which is typical of skeletally immature patients, played an important role in contributing toward β -tricalcium phosphate bone substitute integration and bone healing [23].

Table 3 Literature review of chronic osteomyelitis (CO) in children

Work	Country	Cases (n)	Mean age	Surgical Method used	Causative agent	FU (years)	Results	Complications
Bassey et al. [28]	Nigeria	41	11.9 years	Sequestrectomy Muscle flap	<i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i>	2	Complete healing (all cases)	Joint stiffness Limb shortening Pathological fractures
Kucukkaya et al. [4]	Turkey	7	7.2 years	Sequestrectomy External Fixation	N/A	4.6	Excellent (Clinical and radiological outcomes)	–
Paley et al. [8]	USA	9	10 years	Sequestrectomy ALC rods (38 to 753 days)	N/A	–	Excellent (Clinical and radiological outcomes)	Rod fracture (1 case)
Shrestha et al. [3]	Nepal	90	2 years	Sequestrectomy External Fixation Fibular grafting	N/A	–	–	Limb shortening (3 cases) Stiff knee Pin tract infection
Unal et al. [30]	Turkey	22	8 years	Debridement Secondary bone graft (5/8 cases)	MSSA MRSA <i>Pseudomonas Aeruginosa</i> <i>Proteus Mirabilis</i>	4.5	Satisfactory (>50 %)	–
Hoang et al. [29]	Vietnam	6	9.8 years	Debridement Muscle flap (gracilis)	<i>Staphylococcus Aureus</i> <i>Escherichia Coli</i>	6	Satisfactory (100 %)	–
Bar-On et al. [5]	Israel	4	9.3 years	Debridement Lavage, Reaming ALC rods + beads	<i>Staphylococcus Aureus</i> <i>Pseudomonas Aeruginosa</i> <i>Streptococcus Viridians</i>	3.4	–	Superficial abscess Soft tissue defect Pathologic fracture
Mora-Rios et al. [31]	Mexico	1	4 years	Debridement Application of autologous bone graft No ALC	<i>Staphylococcus Aureus</i>	–	Infection controlled Bone healed Function restored	–
Mansour et al. [11]	Liban	1 CO (out of 8 patients)	Induced membrane technique	No ALC	N/A	1–7	Infection controlled Bone healed	–

MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; ALC, antibiotic-laden cement; FU, follow-up; N/A, not applicable

In our series, ALC was prepared during surgery. The cement was shaped to fill the bone defect, and once it began to stiffen, it was placed in the bone. In order to increase local availability, small pits were made with a K-wire to increase surface area [1]. Moreover, the medullary canal was always reamed.

The ALC spacer induced periosteal membrane formation and provided local antibiotic treatment by delivering a high concentration of antibiotic to the infected zone with less systemic toxicity, as described by Bucholz et al. [24, 25]. As the antibiotic diffuses in the surrounding hematoma, which acts as a transporter, drain application is not recommended [1]. However, although our patients were young and healthy, with normal renal function, caution is warranted in elderly patients or in cases of renal failure [12, 26–28].

Local antibiotic delivery can be successfully obtained with ALC beads, as reported by Whalig and Bucholz [29], Cho et al. [30], and Walenkamp et al. [31]. However, beads offer no mechanical support to the bone and only suboptimal membrane formation and can be difficult to remove as they are enveloped within the surrounding fibrous tissue. The other disadvantage is the challenge of preparing small-enough oval-ended beads for feeding on steel wire to facilitate removal, in the short time window before the cement hardens [13, 23, 24, 30–33].

Our relatively novel approach is shown to be safe, with eradication of the infection, consolidation of bone, and good functional outcome in skeletally immature patients with CO and infected nonunion of the long bones.

Paley et al. [8] and Bar-On et al. [5] reported two series of skeletally immature patients with CO treated surgically by debridement and lavage, reaming of the intramedullary canal, and insertion of gentamicin-impregnated ALC rods into the canal. The primary objectives of using the intramedullary ALC rods were to provide mechanical support to the bone and local antibiotic delivery. The technique was successful in eradicating the infection, although the authors reported two cases of pathological fracture (one case per series) [5, 8].

More recently, Mansour and Ghanem [11] reported preliminary results on the two-step induced membrane technique in eight children. Outcome was good in all but two patients, and the results showed the feasibility of the technique in children. However, it is difficult to compare their technique here as their patients carried heterogeneous diagnoses: congenital pseudoarthrosis (four cases), tumor (three cases) and CO (one case). Mansour and Ghanem identified chemotherapy, suboptimal fixation, and axial malalignment as risk factors for failure. Compared to Mansour and Ghanem's work, our group of patients was more homogeneous in terms of diagnosis. None of our patients had chemotherapy, the extremity was protected

with a plaster cast when long bones were involved, and no pathological fractures occurred in our case series [11].

Another surgical option is to enrich the infection area by augmenting blood supply using a muscle flap. Bassey et al. [34] and Noang et al. [35] have evaluated the efficacy of muscle flaps in the treatment of CO in children and adolescents (Table 3). Although successful, the technique is not free of complications and reported disadvantages include donor site morbidity, adjacent joint stiffness, and/or long scars [33–35]. Moreover, Bassey et al. [34] reported a relatively high incidence of limb shortening and pathological fractures.

There are limitations to the results analyzed here. This was a retrospective case series study reporting preliminary results on a limited number of patients. Even so, the number of patients included in the study was similar to the average number of cases in other published studies that have investigated outcome of CO and infected nonunion managed with ALC [5, 8]. The patients also formed a heterogeneous group in terms of age, type of fracture, and type of chronic infection. Nevertheless, the results are encouraging and our preliminary findings show the feasibility of using ACL in the treatment of CO and infected nonunion in skeletally immature patients. Further work is now needed to confirm our results.

Conclusion

CO is a relatively uncommon disease in the pediatric population. Once discovered, it should be treated promptly. Debridement, sequestrectomy, then use of ALC spacer inducing periosteal membrane formation followed by placement of β -tricalcium phosphate bone substitute into the induced membrane give satisfactory outcomes in skeletally immature children presenting CO and infected nonunion of the long bones.

Acknowledgments Institutional review board approval: The study was approved by the Clermont-Ferrand University Hospital Review Board.

Funding None of the authors received financial support for this study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest in this research.

Ethical approval All procedures and studies involving human participants were performed in accordance with the ethical standards of the national and/or institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent No patients were involved. This is a retrospective study of patient's data for which IRB approval was obtained.

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