Management of infected nonunions by using antibiotic-impregnated bone cement

Rashed E. Rashed, Mohamed A. Nigm, Mohamed A. Elaziz,
Elsayed Shaheen, Mohamed R. Kandeel

Orthopaedic Department, Faculty of Medicine (Males), Al-Azhar University, Cairo, Egypt

Correspondence to Rashed E. Rashed, MD, 6th October City, District 3 Neighborhood 4, st 30, Building 776, Cairo, Egypt,
Tel: 01001128160;
e-mail: rashedelsadek@hotmail.com

Received 31 March 2016
Accepted 24 April 2016

The Egyptian Orthopaedic Journal
2016, 51:26–34

Background
In patients with infected nonunion the primary goal is eradication of infection, before achieving union. Release of antibiotics from bone cement at a higher concentration prevents bacterial growth and formation of biofilm by bacteria. Penetration of antibiotics to the surrounding tissue, including cortical and cancellous bone, prompted the use of antibiotic cement in the control of bone infection.
Patients and methods
This was a prospective study of 12 patients with infected nonunions managed with antibiotic-impregnated bone cement who were followed up for an average period of 1.2 years, with encouraging results. The infected fracture site was exposed and thorough debridement done. The implant was replaced with vancomycin and clindamycin-impregnated cement following adequate debridement. Culture and sensitivity was done for the debrided tissues to identify the pathogen and sensitive antimicrobial agent. Follow-up was performed clinically, radiologically, and using laboratory investigations (by complete blood cell count, erythrocyte sedimentation rate, C-reactive protein).
Results
Infection was eradicated in all patients except one after an average period of 9 weeks (range: 6–14 weeks). Culture revealed no growth and discharge disappeared at the end of this period. Cement was removed after an interval of 6–12 weeks after control of infection and was replaced with definitive fixation with or without bone grafting.
Conclusion
Management of infected nonunions using antibiotic-impregnated cement is a simple and very effective method that allows infection control and promotes bone union. This simple procedure is encouraging, cost effective, and less cumbersome.

Keywords:
antibiotic cement nails, infected nonunions, vancomycin

Egypt Orthop J 51:26–34

1110-1148

Introduction

Infected nonunion of long bones is a chronic and debilitating disorder that still poses a very complex problem to the surgeon today in terms of cost and time-effective treatment. Traditionally, treatment of infected nonunion follows a two-stage procedure. The first stage comprises debridement with or without antibiotic cement bead insertion and systemic antibiotics to convert an infected nonunion to an aseptic nonunion. The second stage is performed to achieve stability by either external or internal fixation and bone grafting [1].

The two-stage technique uses induced biologic membranes with delayed placement of bone graft to manage fracture with bone defects. In the first stage, a polymethylmethacrylate (PMMA) spacer is placed in the defect to produce a bioactive membrane, which appears to mature biochemically and physically 4–8 weeks after spacer placement. In the second stage, cancellous autograft is placed within this membrane and, through elution of several growth factors, the membrane appears to prevent graft resorption and promote revascularization and consolidation of new bone. Excellent clinical results have been reported, with successful reconstruction of bone defects more than 20 cm [2].

According to Gustilo [3] problems associated with infected nonunion are avascularity at the fracture site due to scarring and cicatrization due to multiple surgeries, drug resistance to pathogenic organisms, restriction of neighboring joint motion, and gap

DOI: 10.4103/1110-1148.194432

nonunion. Infection creates an unfavorable environment for fracture healing, especially when it is associated with mechanical instability [4]. Excellent knowledge of the pathophysiology of lesions and the biomechanical concept of fixation techniques is essential for better functional outcome [1].

Infected nonunions have traditionally been treated with external or internal fixation. However, a high prevalence of pin-site infections, muscle contractures, and joint stiffness has been observed in association with external fixation. Some patients might not consent to the use of external fixators, whereas others might not be ideal candidates for external fixation because of obesity or an expectation of poor compliance. The use of antibiotic-impregnated cement benefits these patients. The safety of local antibiotic therapy has been documented in clinical studies. Both animal and clinical studies have shown high local concentrations and undetectable or very low serum levels of the locally delivered antibiotics without systemic toxicity [5].

The use of antibiotic cement-impregnated intramedullary nails (ACIIN) has been described in the literature. Use of ACIIN was first reported by Paley and Herzenberg [6] and later by other authors. ACIIN can provide stability, is easy to remove, and provides all the advantages of cement beads. A high local concentration of antibiotics and low systemic side effects are the major advantages [1].

The aim of our study was to evaluate the effectiveness of antibiotic-impregnated bone cement in the management of infected nonunions for infection control.

Patients and method

The study protocol was approved by the ethics committee of faculty of medicine, Al-Azhar University. This prospective study was conducted from July 2012 to May 2014. Inclusion criteria were infected nonunions with no evidence of union by 6–8 months, with or without bone loss. Patients with multiple medical comorbidities and those with hypersensitivity to vancomycin were excluded from the study. All patients were thoroughly investigated and evaluated by clinical and radiological means.

Twelve cases of infected nonunion (Table 1) were included in our study for treatment of infected nonunion with antibiotic-impregnated cement and to evaluate the results. There were 10 male and two female patients between the ages of 8 and 46 years with a mean age of 27 years. The 12 cases were treated with antibiotic-impregnated cement as the primary procedure after debridement, reaming, and lavage of the medullary canal. All cases were treated with a second-stage stabilization after removal of the bone cement and fixation with K-wires, interlocking nails, plates and screws, or an external fixator with or without cancellous bone grafting after control of the infection.

Four cases had sustained closed fractures, two cases were grade I open fractures, two cases were each of grade II and IIIA open fractures, and the remaining four cases had sustained grade IIIB fractures. There were two cases of infected nonunited femur, two cases of tibia, two cases of humerus, two cases of ulna, one case of radius, and three cases of phalangeal fracture (Table 1). Out of the 12 cases, six had cavitary bone defect, dour had segmental bone defect, and two had no defect. Two patients had intramedullary nail *in situ* when they presented, four patients had an external fixator, three patients had K-wire fixation, and three patients had no implant.

The mean interval from infection to presentation was 8.5 months (range: 6–14 months). All patients had draining sinuses and nine patients were culture positive for

Table 1 Twelve patients with infected nonunion

Age (years)	Sex	Bone involved	Bone defect	Classification	Initial treatment	Duration of infection (months)
43	F	Femur	Cavitary	Closed	Deb./splint	7
36	F	Humerus	Segmental	Open I	Deb./IM rod	8
8	M	Tibia	Cavitary	Open II	Deb./ex. fix.	9
20	M	Thumb	Cavitary	Open IIIA	Deb./K-wire	12
46	M	Phalanx	Cavitary	Open IIIB	Deb./K-wire	7
23	M	Phalanx	Cavitary	Open IIIB	Deb./K-wire	6
28	M	Femur	Segmental	Open IIIB	Deb./ex. fix.	14
26	M	Radius	Segmental	Open IIIB	Deb./ex. fix.	8
21	M	Ulna	Segmental	Closed	Deb./IM rod	6
25	M	Ulna	Cavitary	Closed	Deb./Ex. fix.	11
18	M	Humerus	No	Closed	Deb./splint	7
16	M	Tibia	No	Open I	Deb./splint	9

Deb., debridement; Ex. fix., external fixator; F, female; IM, intramedullary; M, male.

Staphylococcus aureus. The remaining three patients were culture negative. All patients were receiving antibiotics at the time of presentation. Before surgery, antibiotics were started according to culture and sensitivity reports, and in culture-negative patients broad-spectrum Gram-positive and Gram-negative antibiotics were started.

Anteroposterior and lateral radiographs were taken at the time of admission into the study and after the first procedure of cement implantation and after the second procedure involving stabilization at regular intervals of 4 weeks.

Operative procedure

Stage I

Application of antibiotic-impregnated cement: the surgical technique involves a series of steps, each of which is critical for successful results.

Step I (debridement): The first step involves thorough debridement of the infected bone and soft tissues and copious lavage (Figs. 1 and 2). The goal of meticulous debridement was to achieve the viable environment around and at the fracture site. Excision of sinus tracts and of scarred and infected soft tissue was performed to trigger active bleeding in the area surrounding the fracture ends. Implants were removed, as a biofilm is formed around the implant by the bacteria that protect them. Infected avascular bony ends were resected until punctate bleeding surface was observed at the cut end, which is known as Paprika sign.

Step II: The two bone ends were reamed until the fresh bleeding bone was reached to remove small medullary sequestra and infected granulation tissue. The reaming and granulation tissue was sent for culture and sensitivity. The wound and entire intramedullary

Figure 1

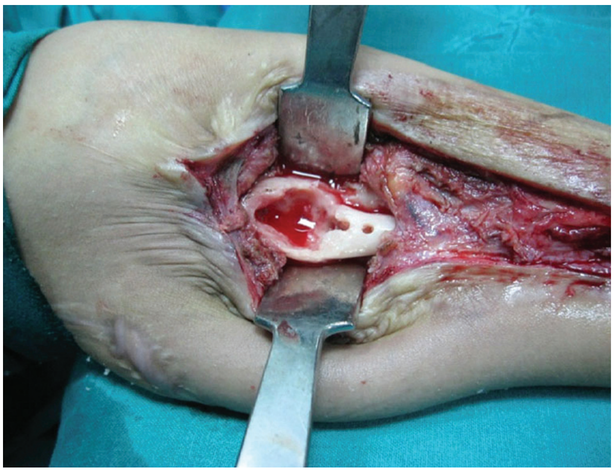
(a) Clinical photography of infected nonunion of the ulna. (b) After exposure of the nonunion site, the infected devitalized tissues appeared canal were cleaned with normal saline. To a great extent the infected nonunion was converted into an aseptic nonunion (Fig. 3).

Step III: Preparation of antibiotic-impregnated indigenous cement: after the surgical team had changed their gowns and gloves the limb was prepared again and re-draped before antibiotic-impregnated cement was prepared. Antibiotic cement was prepared with 4 g of antibiotic and 40 g of PMMA cement. The antibiotics used were vancomycin and gentamicin or clindamycin (Fig. 4). If more than 4 g of antibiotic is used the cement becomes brittle. The antibiotic cement was kept in air for evaporation of the monomer.

Antibiotic-cemented nail preparation: It is performed manually on a separate table taking all aseptic measures (Fig. 5). K-nails (for cases with femur nonunion) of diameter 2–3 mm thinner than the last reamer width were chosen. PMMA bone cement of 40 g was mixed with 4 g of vancomycin powder or clindamycin cap. Monomer solution was added to this powder and mixed until the material acquired viscous consistency. The antibiotic cement was then applied uniformly over the wire and the cement was allowed to set. The diameter of the cement nail was checked, excess cement was shaved off, and the nail was rerolled before the cement set. Bone cement is allowed to set for 15 min before insertion to prevent cement nail debonding.

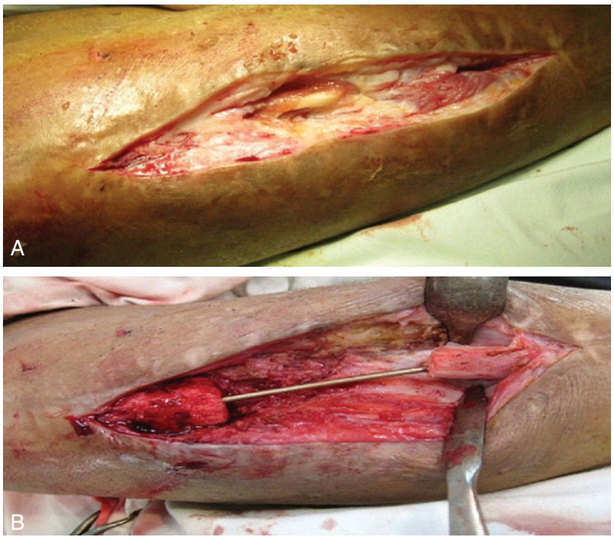
Step IV: Application of antibiotic-impregnated cement: antibiotic-impregnated cement was inserted into the bone defect and in the cavity inside the medullary canal (Figs 6 and 7). In case of antibiotic-cemented nail the bone ends aligned and the nail was inserted.

Figure 2



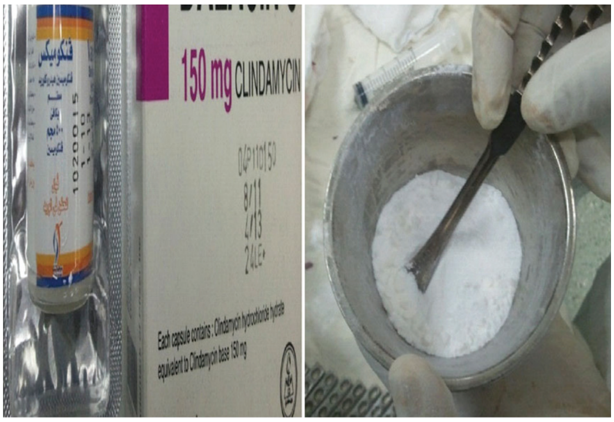
Debridement of infected bone and of devitalized tissues in infected nonunited radius fracture.

Figure 3



(a) Infected nonunion site of ulna fracture. (b) After debridement of devitalized tissues and excision of infected bone ends, reaming of the medullary canal and provisional stabilization of the fracture with an intramedullary rod.

Figure 4



Preparation of antibiotic-impregnated cement.

Figure 5

Preparation of antibiotic-cemented nail.

Step V: Provisional stabilization of the fracture: if the fracture was unstable after antibiotic-impregnated cement insertion we performed provisional stabilization using a K-wire, intramedullary rod, or external fixator.

Step VI: Hemostasis was secured and the wound was closed in layers over a suction drain.

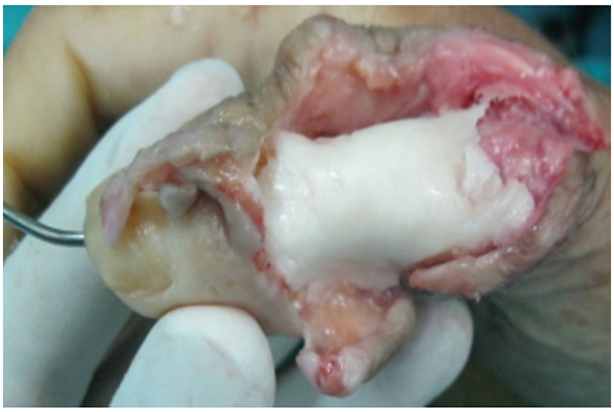
Postoperative management: The patient was kept on appropriate intravenous antibiotics after culture report for 2 weeks, followed by oral antibiotics for 4 weeks. Follow-up included complete blood cell count, erythrocyte sedimentation rate, and C-reactive protein for activity of infection.

Antibiotic cement removal: Once the infection was controlled, the antibiotic bone cement was removed at ~4–6 weeks after implantation (Fig. 8). If the infection was uncontrolled, on the basis of laboratory parameters and clinical evaluation, the patient was treated repeatedly following the same protocol until the culture report of medullary canal and reaming was negative. After control of infection, definitive surgery was performed in stage II to achieve union.

Figure 6

Application of the antibiotic-impregnated cement in the bone defect in infected nonunited ulna after complete debridement and lavage of the wound.

Figure 7

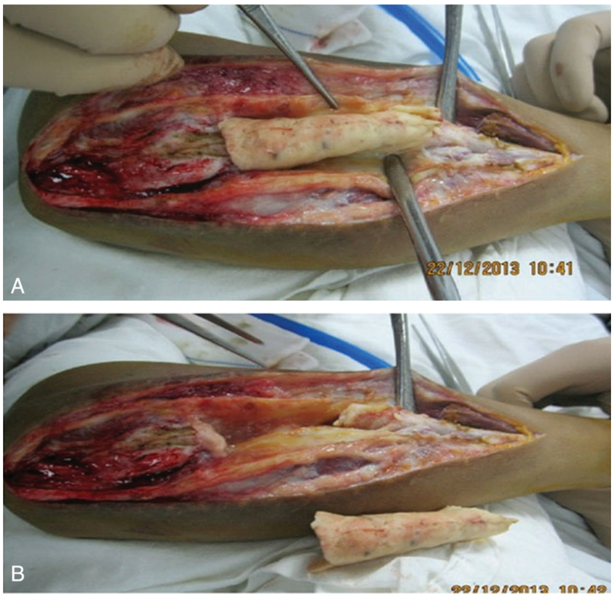


Insertion of antibiotic-impregnated cement in infected nonunion of the thumb.

Stage II – definitive stabilization

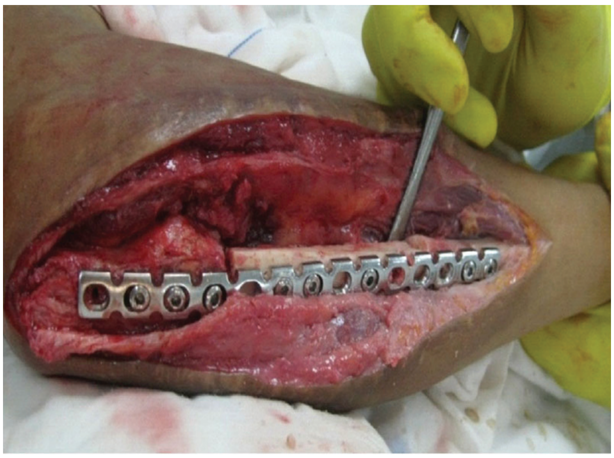
After stage I the limb was followed up and radiographs were taken every 4 weeks. Infection status was evaluated by laboratory investigations like complete blood cell count, erythrocyte sedimentation rate, and C-reactive protein. If the infection was controlled

Figure 8



(a, b) Removal of antibiotic bone cement after eradication of infection in infected nonunion of the ulna.

Figure 9



Definitive open reduction and internal fixation (ORIF) of the fracture with bone grafting of the defect.

showing signs of subsidence (clinical, radiological, and laboratory), stage II surgery was performed. Stage II surgery included definitive stabilization with or without bone grafting (Figs 9 and 10).

Results

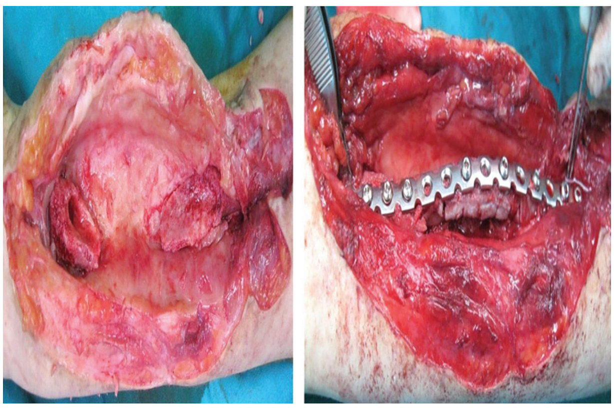
Twelve cases of infected nonunion were included in our study for treatment with antibiotic-impregnated indigenous cement and to evaluate the result. The average duration of follow-up was 14 months (range: 6–20 months).

Outcomes of the study were analyzed in terms of success and failure (Table 2). Successful cases were those with complete clinical, radiological, and laboratory eradication of infection. Failure cases were those in which the infection did not subside. The most common microorganism isolated in our study was *S. aureus*.

Eleven of 12 (91.6%) patients in our study who underwent antibiotic-impregnated cement application achieved infection control at an average duration of 9 weeks (range: 6–14 weeks) and had clinical, radiological, and laboratory signs of eradication of infection (Figs 11–13). These patients were continued with antibiotic cement until second-stage stabilization. Consequently, all 11 patients underwent cement removal and definitive stabilization.

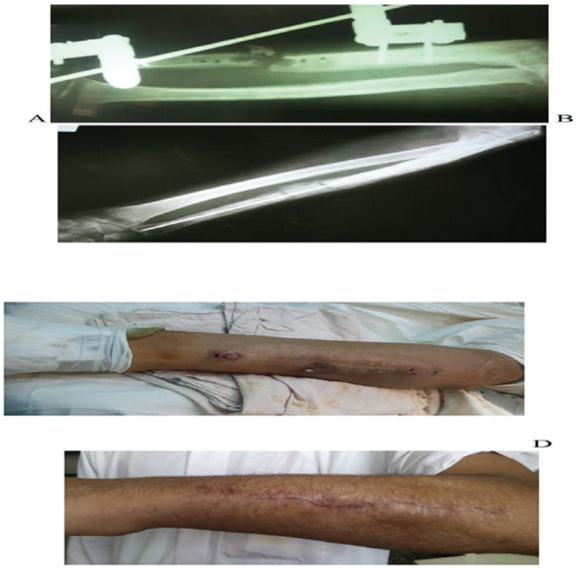
Out of 11 cases second stabilization was done after 6–9 weeks (average: 6.5 weeks) after control of the infection. The cement was removed and nine cases needed autogenous corticocancellous bone graft. The remaining two cases did not need bone grafting.

Figure 10



A case of infected nonunion of the radius. (a) After removal of the bone cement; (b) after bone grafting and definitive fixation.

Figure 11



A 25-year-old male patient with infected nonunited fracture of the ulna for 11 months' duration. (a) Preoperative radiograph of the nonunion with a defect. (b) Plain radiograph 6 weeks after the procedure, showing the cement in the nonunion gap. (c) Preoperative photograph showing the draining sinus with exposed part of the bone and pin-tract infection due to external fixator. (d) Photograph of the limb 6 weeks after the procedure with complete eradication of the infection and healing of the wound and absence of draining sinuses.

Table 2 Results of twelve patients with infected nonunion treated with antibiotic-impregnated cement

Case numbers	Bone	Bone defect	Infection control	Duration of infection control (weeks)	Secondary procedures
1	Femur	Cavitary	Failure	–	Antibiotic cement nail
2	Humerus	Segmental	Controlled	10	Plate and screws+BG
3	Tibia	Cavitary	Controlled	9	Ms flap+splint
4	Thumb	Cavitary	Controlled	6	BG+K-wires
5	Phalanx	Cavitary	Controlled	9	BG+K-wires
6	Phalanx	Cavitary	Controlled	12	BG+K-wires
7	Femur	Segmental	Controlled	6	ILFN+BG
8	Radius	Segmental	Controlled	10	Plate and screws+BG
9	Unla	Segmental	Controlled	12	Plate and screws +fibular BG
10	Unla	Cavitary	Controlled	14	Plate and screws+BG
11	Humerus	No	Controlled	12	Plate and screws+BG
12	Tibia	No	Controlled	8	Splint

BG, bone graft; ILFN, interlocking femoral nail.

Three cases needed definitive fixation with K-wires, five cases with plates and screws, one case with an interlocking nail, and two cases with a splint. Overall, 11 cases achieved infection control at the last follow-up.

Failure

There was only one (8%) case of femur nonunion in which the patient had undergone debridement and filling of the defect with bone cement in the first operation. The infection was not controlled by 16 weeks of follow-up. The patient underwent cement removal and debridement and insertion of antibiotic-cemented nail. By 12 weeks the infection had subsided and definitive fixation and bone grafting was done.

Figure 12

8 years old boy with infected nonunion for 9 months duration after type II open fracture of the proximal tibia. Debridement and antibiotic impregnated cement implantation was done. After 8 weeks cement was removed, bone grafting, muscle flap and skin graft was done for soft tissue coverage. Plain radiograph 8 weeks after the second procedure revealed union of the fracture with complete eradication of the infection.

Discussion

Osteomyelitis is not a rare problem, and most cases are because of surgical infections or subsequent antecedent open fractures. Managing recalcitrant osteomyelitis often requires the combination of local and systemic treatments. The ultimate goals of management are eradication of infection, prevention of recurrence, and maintenance of optimal limb function. The literature on osteomyelitis treatment emphasizes the importance of extensive surgical debridement in eliminating these infections. However, surgical

Figure 13

A 20 years old male patient with infected nonunited fracture of the radius, (A&B) preoperative radiography, (C&D) radiography 6 months after the definitive procedure with complete union of the fracture.

debridement and systemic antibiotic treatment without local antibiotic augmentation are associated with a higher rate of recurrence and subsequent operations. Repeated surgeries often deteriorate the already compromised condition of the soft tissue and local blood supply, which may diminish the level of antibiotic penetration. A higher complication rate and poor limb function usually jeopardize such limb-salvaging procedures [7].

The concept of local delivery of antibiotics to manage osteomyelitis was developed in the early 20th century in an effort to increase local antibiotic concentrations [8]. Various delivery vehicles for antibiotics are currently available, including PMMA cement and several types of biodegradable bone fillers. PMMA cement, however, is the most commonly used and cost-effective delivery material. After being mixed into the PMMA cement, antibiotics are steadily released from the cement's surface and from cracks and voids in the cement [9]. In one study evaluating antibiotic concentration of the joint fluid in total hip arthroplasties fixed with antibiotic-loaded PMMA cement, the authors showed that, although most antibiotic release occurred within the first 9 weeks, a slow liberation through cracks was found to persist for 10 years after the original procedure [10].

Osteomyelitis is commonly polymicrobial in 70% of patients. The most common infecting organism in the literature and in our study was *S. aureus*. Gentamicin and vancomycin are common choices for local delivery of antibiotics because of their broad spectrum of activity, heat stability, and low allergenicity. Clinical and experimental studies show them to have good elution properties from bone cement and to have no deleterious effects on bone healing [1]. Since first being isolated and reported on in 1961, the rate of methicillin-resistant *Staphylococcus aureus* (MRSA) infection has risen dramatically and is currently the leading pathogen of skeletal infections. Among those antibiotics effective in treating MRSA-related infection, vancomycin is considered the standard agent. Consequently, more orthopedic surgeons use vancomycin against MRSA before identifying the causative organism [7].

Klemm [11] was the first to use antibiotic beads in case of osteomyelitis. However, placement of intramedullary antibiotic bead chains in the medullary canal is cumbersome for placement of external fixators, as the chain cannot be introduced after pin placement. Moreover, if placed before the pins, the chains cannot be removed easily. It provides no mechanical support for the fracture and cannot fill up the dead space completely. Furthermore, in-growth of granulation tissue between the beads makes it difficult to remove the beads after being kept in place for more than 2 weeks [4].

To overcome the problem of cement beads some authors began using self-made antibiotic-impregnated cement rods to treat infection of tibial fractures after nailing, and good results were obtained [6,12]. In comparison with antibiotic-impregnated cement beads, cement rods have enough intensity and proper diameter and can be easily inserted to fill up nearly all of the dead space. The side effect and amount of antibiotics can be reduced because of high antibiotic concentration in the local site [4].

Thonse and Conway [13] have studied 20 cases of infected nonunion with bone defect. They had achieved union by primary use of antibiotic-impregnated cement nail in two cases with bone defect, with the remaining cases requiring a secondary procedure. They reported infection control in 95% of their cases. Chen *et al.* [14] and Babhulkar and Pande [15] achieved 100% union in their series by following a two-stage procedure. There were no patients with persistent infection. Shahcheraghi and Bayatpoor [16] also found 100% union in his series, especially in patients treated with intramedullary nailing and bone grafting. He also encountered 33% persistent infection in his series.

In our study 11 patients had achieved control of infection through a single-stage procedure with the use of antibiotic-loaded bone cement, of whom two patients did not have any bone defect, six patients had cavitary bone defect, and three patients had segmental bone defect. The remaining patient had persistent infection and was treated with antibiotic-impregnated cement nail as the primary procedure, followed by a secondary procedure. Infection could be controlled in 11 (91.7%) cases by this technique and could not be controlled in one (8.3%) case.

Conclusion

Infected nonunion can be treated effectively if we follow the correct protocol from debridement with provisional stabilization to secondary fixation with or without bone grafting after control of infection with antibiotic-impregnated cement nails. Conversion of septic nonunion to aseptic nonunion is the main step of the protocol. Indigenous antibiotic-impregnated cement is an ideal modality of treatment to achieve the union.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1 Dhanasekhar R, Jacob PJ, Francis J. Antibiotic cement impregnated nailing in the management of infected non-union of femur and tibia. Kerala J Orthop 2013; 26:93–97.

2 Taylor BC, French BG, Fowler TT, Russell J, Poka A. Induced membrane technique for reconstruction to manage bone loss. J Am Acad Orthop Surg 2012; 20:142–150.

3 Gustilo RB. Management of infected fractures. Surg Musculoskeletal Syst 1990; 5:4429.

4 Galfat DR, Agnihotri A, Bansal A. Management of infected non union of long bones with antibiotic impregnated cement nail. Natl J Med Dental Res 2013; 1:25–32.

5 Thonse R, Conway JD. Antibiotic cement-coated nails for the treatment of infected nonunions and segmental bone defects. J Bone Joint Surg Am 2008; 90(Suppl 4):163–174.

6 Paley D, Herzenberg JE. Intramedullary infections treated with antibiotic cement rods: preliminary results in nine cases. J Orthop Trauma 2002; 16:723–729.

7 Fan C-Y, Hsieh M-S, Chen W-M, Chen C-F. Successful management of infected intramedullary nailing with reaming, lavage, and insertion of antibiotic-impregnated cement rods. J Exp Clin Med 2011; 3:137–141.

8 Wininger DA, Fass RJ. Antibiotic-impregnated cement and beads for orthopedic infections. Antimicrob Agents Chemother 1996; 40:2675–2679.

9 Masri BA, Duncan CP, Beauchamp CP. Long-term elution of antibiotics from bone-cement. An in vivo study using the prosthesis of antibiotic-loaded acrylic cements (PROSTALAC) system. J Arthroplasty 1998; 13: 331–338.

10 Powles JW, Spencer RF, Lovering AM. Gentamicin release from old cement during revision hip arthroplasty. J Bone Joint Surg Br 1998; 80:607–610.

11 Klemm KW. Antibiotic bead chains. Clin Orthop Relat Res 1993; 295:63–76.

12 Ohtsuka H, Yokomaya K, Higashi K, Tsutsumi A, Noumi T. Use of antibiotic-impregnated bone cement nail to prevent septic nonunion after open tibial fractures. J Trauma 2002; 52:364–366.

13 Thonse R, Conway J. Antibiotic cement-coated interlocking nail for the treatment of infected nonunions and segmental bone defects. J Orthop Trauma 2007; 21:258–268.

14 Chen CE, Ko JY, Wang JW, Wang CJ. Infection after intramedullary nailing of the femur. J Trauma 2003; 55:338–344.

15 Babhulkar S, Pande K. Nonunion of the diaphysis of long bones. Clin Orthop Relat Res 2005; 431:50–56.

16 Shahcheraghi GH, Bayatpoor A. Infected tibial nonunion. Can J Surg 1994; 37:209–213.