Comparison of various surgical methods in the treatment of implant-related infection

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Abstract The treatment of implant-related infections is troublesome. This study was conducted to compare the effectiveness of three different surgical modalities in the treatment of implant-related infection. A total of 32 Wistar albino rats were randomised into four groups after the establishment of implant-related infection: no treatment, surgical débridement, antibiotic-loaded bone cement and antibiotic-loaded autogenous bone. Microbiological colony counts were made at the sixth week in order to evaluate the effectiveness of the treatments. The antibiotic-loaded bone cement group revealed superior results compared with the other groups in terms of reduction of microbiological colonies. Three animals in the bone cement group revealed extensive infection. Although antibiotic-loaded bone cement showed superiority over other treatment modalities, it should be employed after an unsuccessful trial of débridement because of the risk of extensive infection.

Introduction

Bone infections associated with foreign bodies such as prostheses and other osteosynthetic devices are especially difficult to treat. Implant-related infections may result in prolonged hospitalisation, poor functional status and sepsis [1, 2]. *Staphylococcus aureus* is a common organism that causes deep wound infection after orthopaedic operations [1, 3]. *S. aureus* is known to secrete a number of surface-associated proteins that are potent stimulators of bone resorption [4]. *S. aureus* is also capable of producing a protective exopolysaccharide biofilm which plays a major role in infection especially with respect to treatment, even though its role in the development of infection is weak [5]. The use of local antibiotic delivery systems, especially antibiotic-loaded bone cement, is a well established procedure in the treatment of musculoskeletal infections [6–11]. On the other hand, antibiotic-loaded cement beads have several disadvantages including the need for a second operation to remove the cement beads and the possibility of local immune compromise [8, 9].

Even though many researchers have reported that local biodegradable antibiotic carriers are effective in in vivo conditions, the in vitro results are not well documented. The related literature reports have revealed contradictory results about the effectiveness of these bioabsorbable materials. Moreover, most of these materials are incapable of mechanical loading and despite their in vitro effect there are difficulties involved in the in vivo application. Zelken et al. stated in their in vivo study that the poor handling properties of hydroxyapatite paste prevent its in vivo use against infection [7]. Many recent studies have shown that autogenous bone can also be used as an antibiotic carrier in the local control of musculoskeletal infections [12–13]. Antibiotic-loaded bone grafts have been shown to elute

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effective antibiotic concentrations over a long period. In addition, autogenous bone has been shown to restore bone defects and promote bone healing in clinical studies [14]. To our knowledge, this is the first study comparing antibiotic-loaded autogenous bone and other treatment modalities in the treatment of implant-related osteomyelitis using a model.

Therefore, in the setting of an animal study, the objective of this investigation was to evaluate the efficacy of different surgical modalities when deep infection occurs after intramedullary stabilisation of fresh fractures in rat tibias.

Materials and methods

The study was approved by the local Ethics Committee of Dokuz Eylül University. The experiment was conducted using 32 female 6-month-old Wistar albino rats. The animals weighed approximately 200–250 g at the beginning of the study. The animals were given free access to food and water during the study. The surgery was performed under general anaesthesia by intraperitoneal administration of 60 mg/kg ketamine and 10 mg/kg xylazine. The left legs of the animals were shaved and disinfected with alcohol and covered with sterile drapes and sheets before the surgery.

Bacteria and preparation of inocula

S. aureus (ATCC 25923 standard strain) was obtained from the Microbiology Department of İzmir Atatürk Training and Research Hospital. The *S. aureus* strain used is a standard strain obtained from frozen stock cultures. The bacterium has a sensitivity to vancomycin and teicoplanin. Using a sterile loop well-isolated colonies were picked and suspended into 2 ml of tryptic soy broth (TSB). Thereafter they were incubated aerobically at 35°C for 4–5 h until a 0.5 McFarland turbidity standard was reached [1×10^7 to 1×10^8 colony-forming units (CFU)/ml]. After that 100 µl bacteria solutions were transferred into 10 ml phosphate-buffered saline (PBS). The bacterial solution obtained was 1×10^5 to 1×10^6 CFU/ml.

Operation

The skin and fascia at the anteromedial tibia were incised approximately 1 cm in length. The periosteum was incised and the tibial shaft was exposed. After that the tibias were fractured transversely by the aid of a mini osteotome. The proximal tibial metaphysis was surgically exposed in order to gain access to the medullary cavity. We created a 1-mm hole at the proximal metaphysis using a burr and the diaphysial fractures were fixed intramedullarily with Kirschner wires (0.8 mm diameter). PBS containing 10^3 CFU/10 µl of *S. aureus* was injected into the medullary cavity at the fracture

site. The extraneous parts of the Kirschner wires were cut off at the site of entry [15–18].

Swab cultures were obtained from the operation sites at the first week to confirm the establishment of deep infection. The original surgical incisions were used to inspect the infection field. The cotton tip of the swab was swiped completing a tour on the infected tibias and then inoculated on culture media immediately. Microbial cultures were made by conventional methods. Briefly, swabs were applied to 5% sheep blood agar plates and incubated at 37°C. After 24 hours incubation microbial colonies on agar plates were identified by a fully automated laboratory system (Phoenix, Becton Dickinson, Franklin Lakes, NJ, USA). *S. aureus* growth rates were determined and continued to be studied. A positive infection was defined if the colony count exceeded ten colonies. Only one animal (control group) was excluded from the study because of a negative microbiological result. Another animal in which deep infection was established was included in the study so that there were eight animals in each group.

Treatment groups

At the third week the animals were randomised into four groups and different treatment protocols were performed for each group.

- Group 1: (control) no treatment
- Group 2: surgical débridement + intramuscular (i.m.) teicoplanin (20 mg/kg per day) (Targocid® 400 mg sterile powder, Aventis) for 14 days
- Group 3: surgical débridement + teicoplanin embedded polymethylmethacrylate (PMMA) beads + i.m. teicoplanin (20 mg/kg per day)
- Group 4: surgical débridement + teicoplanin embedded autogenous bone grafts + i.m. teicoplanin (20 mg/kg per day)

Preparation of autogenous grafts

The autogenous bone grafts were obtained from the supracondylar femoral region. A 1-cm lateral incision was used to expose the lateral femoral condyle of the fractured extremity and then a cortical hole of approximately 1 cm in diameter was created with a burr and corticocancellous grafts were taken using a small curette. Morsellised bone specimens were washed and dried before the impregnation process. Thereafter the bone grafts were embedded in antibiotic solution. Briefly, 5 g of morsellised bone was impregnated with 5 ml of antibiotic solution for one hour at room temperature. Finally, bone graft material was placed at the fracture site after surgical débridement was undertaken.

At the sixth week the animals were sacrificed.

Evaluation of study results

The fracture healing was evaluated macroscopically and radiologically after the animals were sacrificed. Lateral views of left tibias were taken at the sixth week for radiological evaluation (Fig. 1).

The microbiological evaluation was undertaken in terms of counting CFU per 1 g of bone obtained at the fracture site. Bacterial growth control and colony count were made by a quantitative culture method. An infected 1-g bone sample was put into 1 ml PBS and then vortexed for 2 min. Quantitative culture was made from this suspension and incubated 24 hours at 37°C. After incubation, the colony count was made. The results of the microbacterial evaluation are shown in Table 1.

Statistical evaluation

The results were analysed using the Mann-Whitney U test. All parameters were summarised by means of a 95% confidence interval (CI), graphics and tables. Significance was set at $P < 0.05$.

Results

All of the surgical treatment groups (groups 2, 3 and 4) showed superior results compared with the control group (group 1) in reducing the number of bacterial CFU/g of harvested bone. There was no significant difference between group 2 (débridement) and group 4 (débridement + antibiotic embedded autogenous graft). There was a statistically significant difference between group 2 (débridement +

Fig. 1 a–d Radiological evaluation of treatment groups at the sixth week. **a** No treatment. **b** Débridement. **c** Autogenous bone. **d** Bone cement

Table 1 Colony count results of the animals in each group

Control	Débridement	Bone cement	Autogenous bone
10^5	10^3	10^3	2×10^2
10^4	10^3	10^3	10^2
10^5	10^4	None ^a	10^4
10^6	10^4	None ^a	10^3
10^6	None ^a	10^2	10^4
10^5	10^2	None ^a	None ^a
10^5	10^4	10^2	10^3
10^5	None ^a	10^2	10^3

^aNo growth of micro-organism

antibiotic-loaded cement) and group 3 and between group 3 and group 4. The P values are summarised in Table 2.

All of the tibias in the control group revealed macroscopic infection and complete union had occurred only in two tibias. All of the tibias in the débridement group were completely healed both macroscopically and radiologically. No macroscopic infection was detected in the débridement group. Three tibias in the antibiotic-loaded autogenous bone group revealed macroscopic infection and purulent drainage. The posterior cortices of the tibias healed radiologically in all animals in the cement group. None of the eight tibias in the antibiotic-loaded cement group revealed complete union and three of them revealed macroscopic infection. Macroscopic and radiological findings of the groups are presented in Table 3.

Discussion

Our study showed that the use of antibiotic-loaded bone cement for the treatment of implant-related infections is superior to other treatment modalities. This result correlates well with recent literature. Many in vitro and in vivo studies have suggested that antibiotic-impregnated PMMA beads are very effective against eradication of infection [7–11]. However, antibiotic-impregnated PMMA beads have certain disadvantages. After the eradication of infection, residual bone defects must be restored. In addition, antibiotic-impregnated PMMA beads become a foreign substance suitable for bacterial colonisation after the antibiotic has been depleted. Therefore, antibiotic-impregnated PMMA

Table 2 The P values presenting statistical comparisons of the groups

	Control	Débridement	Autogenous bone
Débridement	0.01		
Bone cement	0.000	0.01	0.913
Autogenous bone	0.048	0.102	

Table 3 Macroscopic and radiological findings in the different groups

	Control (n=8)	Débridement (n=8)	Bone cement (n=8)	Autogenous bone (n=8)
Radiological findings				
Union	2	8	0	3
Nonunion	6	0	8	5
Macroscopic findings				
Purulent drainage or abscess formation	8	0	3	3

beads must be removed and bone defects must be filled with autologous or allograft bone with an additional surgery [7, 8]. In our study we also observed macroscopically extensive infection in some animals treated with antibiotic-loaded cement beads, whereas no animals in the débridement group showed macroscopic infection. We think that if the infection cannot be eradicated by débridement the cement beads may provide a suitable environment for the spread of infection. Chen et al. and Chan et al. suggest in their respective studies that the use of impregnating antibiotics for infected nonunions have no adverse effects on autogenic cancellous bone graft incorporation and could help to eliminate infection effectively [13, 14]. The hypothesis of our study was that autogenous bone might have provided a better solution for implant-related infection compared with other treatment modalities. However, our results showed that in a rat model antibiotic-loaded autogenous bone is not superior to débridement and systemic antibiotic treatment. This result presents contradictions to the related literature [19, 20]. Our study clearly showed that application of antibiotic-loaded bone does not provide additional advantages in the control of implant-related infection. The fate of antibiotic-loaded bone grafts may be implicated by the uncontrolled local environment in the infection field such as local pH changes and inflammatory reaction. The graft material might have been resorbed too quickly in the infection field without providing antibiotic release for a long duration. Besides, a cortical bone graft may serve as a dead foreign body for bacterial overgrowth just as the bacterial overgrowth on the surface of polyethylene and PMMA.

Experimental osteomyelitis has been used to show the efficacy of different treatment methods in implant-related osteomyelitis. In our animal model, three different surgical modalities were compared in terms of bacterial colony reduction. The use of autogenous bone was preferred in this study because the commercially available bone grafts exhibit antigenicity and evoke an immune response which can alter the results. Also, the denaturing process eliminates the osteoinductive properties of the graft materials. This study revealed that antibiotic embedded autogenous bone is not superior to débridement and parenteral antibiotic administration in implant-related infection. At this point we agree with Kinik et al. that the quality of surgical

débridement is the most important parameter for the success of treatment of bone infections [10].

There are some limitations to our study. The main weakness is the small number of animals used in the experiment. Also, the extent of infection was evaluated only qualitatively in the study model and a pretreatment colony count could not be presented. More studies should be done on this subject which may provide more definitive comparison.

Although antibiotic-loaded bone cement revealed superior results, three animals also revealed macroscopic infection in that group. Therefore, it can be concluded that effective débridement and parenteral antibiotic treatment should be the first step in the treatment of implant-related infections. Antibiotic-loaded bone cement should only be used after two or three unsuccessful attempts at débridement.

References

1. Gristina AG, Costerton JW (1985) Bacterial adherence to biomaterials and tissue. The significance of its role in clinical sepsis. *J Bone Joint Surg Am* 67:264–273
2. Bauer TW, Schils J (1999) The pathology of total joint arthroplasty. II. Mechanisms of implant failure. *Skeletal Radiol* 28:483–497
3. Mader JT, Wang J, Calhoun JH (2001) Antibiotic therapy for musculoskeletal infections. *J Bone Joint Surg Am* 83:1878–9180
4. Lau YS, Wang W, Sabokbar A, Simpson H, Nair S, Henderson B, Berendt A, Athanasou NA (2006) Staphylococcus aureus capsular material promotes osteoclast formation. *Injury* 37(Suppl 2):S41–S48
5. Hudetz D, Ursic Hudetz S, Harris LG, Luginbühl R, Friederich NF, Landmann R (2008) Weak effect of metal type and ica genes on staphylococcal infection of titanium and stainless steel implants. *Clin Microbiol Infect* 14(12):1135–1144
6. Evans RP, Nelson CL (1993) Gentamicin-impregnated polymethylmethacrylate beads compared with systemic antibiotic therapy in the treatment of chronic osteomyelitis. *Clin Orthop Relat Res* 295:37–42
7. Zelken J, Wanich T, Gardner M, Griffith M, Bostrom M (2007) PMMA is superior to hydroxyapatite for colony reduction in induced osteomyelitis. *Clin Orthop Relat Res* 462:190–194
8. Mendel V, Simanowski HJ, Scholz HC, Heymann H (2005) Therapy with gentamicin-PMMA beads, gentamicin-collagen sponge, and cefazolin for experimental osteomyelitis due to Staphylococcus aureus in rats. *Arch Orthop Trauma Surg* 125(6):363–368
9. Kanellakopoulou K, Giamarellos-Bourboulis EJ (2000) Carrier systems for the local delivery of antibiotics in bone infections. *Drugs* 59:1223–1232

10. Kinik H, Karaduman M (2008) Cierny-Mader type III chronic osteomyelitis: the results of patients treated with debridement, irrigation, vancomycin beads and systemic antibiotics. *Int Orthop* 32(4):551–558
11. Günal I, Seber S, Kiraz N, Türkay S, Oztuna V, Göktürk E (1996) In vitro evaluation of antibiotic diffusion from antibiotic impregnated xenografts (in French). *Rev Chir Orthop Reparatrice Appar Mot* 82 (1):59–62
12. Chen CE, Ko JY, Pan CC (2005) Results of vancomycin-impregnated cancellous bone grafting for infected tibial nonunion. *Arch Orthop Trauma Surg* 125(6):369–375
13. Chan YS, Ueng SW, Wang CJ, Lee SS, Chao EK, Shin CH (1998) Management of small infected tibial defects with antibiotic-impregnated autogenic cancellous bone grafting. *J Trauma* 45 (4):758–764
14. Hsieh PH, Chang YH, Chen SH, Shih CH (2006) Staged arthroplasty as salvage procedure for deep hip infection following intertrochanteric fracture. *Int Orthop* 30(4):228–232
15. Tuzuner T, Sencan I, Ozdemir D, Alper M, Duman S, Yavuz T, Yildirim M (2006) In vivo evaluation of teicoplanin- and calcium sulfate-loaded PMMA bone cement in preventing implant-related osteomyelitis in rats. *J Chemother* 18(6):628–633
16. Witso E, Persen L, Benum P, Bergh K (2005) Cortical allograft as a vehicle for antibiotic delivery. *Acta Orthop* 76:481–486
17. Witso E, Persen L, Benum P, Bergh K (2002) Release of netilmicin and vancomycin from cancellous bone. *Acta Orthop Scand* 73:199–205
18. Worlock P, Slack R, Harvey L, Mawhinney R (1988) The prevention of infection in open fractures. An experimental study of the effect of antibiotic therapy. *J Bone Joint Surg Am* 70(9):1341–1347
19. Winkler H, Janata O, Berger C, Wein W, Georgopoulos A (2000) In vitro release of vancomycin and tobramycin from impregnated human and bovine bone grafts. *J Antimicrob Chemother* 46:423–428
20. Lindsey RW, Probe R, Miclau T, Alexander JW, Peren SM (1993) The effects of antibiotic-impregnated autogeneic cancellous bone graft on bone healing. *Clin Orthop Relat Res* 291:303–312