Home-made Local Antibiotic Cement for Chronic Osteomyelitis Caused by Resistant Organisms

Boonsin Buranapanitkit M.D., Suntorn Wongsiri M.D.

Department of Orthopaedic Surgery
Faculty of Medicine, Prince of Songkla University
Haadyai, Songkhla, Thailand

ABSTRACT

Fifteen patients aged between 11 and 47 diagnosed with chronic osteomyelitis due to organisms resistant to gentamicin were treated by combining local home-made local antibiotic cement with an oral antibiotic after thorough surgical removal of necrotic tissue. The most common cause was an open fracture (80%). Femur and tibia were the common sites of involvement. MRSA (Methicillin-resistant *Staphylococcus aureus*) was the causative agent in 8 patients. During the follow-up, ranging from 12 to 84 months, all but one patient had complete control of infection. One patient had recurrence at 5 years but it resolved after repeating the treatment. There was no systemic complication of the antibiotics used. We found that combining appropriate local and oral antibiotics to be effective in controlling infection caused by resistant organisms of chronic osteomyelitis.

INTRODUCTION

Chronic osteomyelitis can be a devastating disease because the treatment is usually time consuming and it can cause many complications including pathologic fractures, limb loss, septicaemia or even death. The aetiology could be due to spread of bacteria via the haematogenous route or as a consequence of trauma, especially in open fractures. The most common causative organism is *Staphylococcus aureus*. However, the incidence of resistant organisms is increasing in many countries[1-6]. Chronic osteomyelitis caused by resistant strains such as MRSA (methicillin-resistant *Staphylococcus aureus*), *Pseudomonas aeruginosa* or enterococci is rarely reported[7,8]. Treatment of chronic osteomyelitis includes both medical and surgical options. Appropriate antibiotics should be used for a minimum of 6 weeks to prevent a risk of recurrent infection. Parenteral antibiotics[9] usually are necessary, especially during the initial period of treatment, but sometimes prolonged antibiotic use is needed due to the insensitivity of the organisms and this can cause adverse side effects such as renal toxicity from aminoglycosides[9].

Correspondence should be sent to :
Dr Boonsin Buranapanitkit
Department of Orthopaedic Surgery
Faculty of Medicine, Prince of Songkla University
Haadyai, Songkhla
Thailand 90110

Local antibiotic cement has been approved for its efficacy as an adjuvant for treating orthopaedic infections[9,10]. Higher local concentration of antibiotic from the local antibiotic cement used can decrease systemic toxicity from parenteral antibiotics[11]. Septopal®, the only commercially available local antibiotic cement is comprised of gentamicin loaded in polymethylmethacrylate. Septopal® has been claimed to eradicate most gram-positive and gram-negative bacterial infections. However, it has been reported to be ineffective in treating osteomyelitis caused by organisms resistant to gentamicin[11]. Home-made local antibiotic cement can be a treatment of choice in these cases. Its beneficial effects are cheapness, ready availability and the ability to modify the type of antibiotic which could be delivered locally to match the appropriate sensitivity of the organisms[9]. Review of the literature indicates that there have been no previous study reporting the results of home-made local antibiotic cement in chronic osteomyelitis caused by resistant organisms.

The objective of this study is to report a series of chronic osteomyelitic patients caused by resistant organisms treated with combined home-made antibiotic cement and oral antibiotics.

MATERIALS AND METHODS

A retrospective study was done on 15 patients diagnosed with chronic osteomyelitis caused by resistant organisms who were admitted to Songkhanagarind Hospital during the period between January 1993 and January 2000. Data included demographics (age, sex, causation, underlying disease, site, type (Cierney-Mader classifications), previous treatment, laboratory investigation (white blood count, ESR erythrocyte sedimentation rate), Bun/Cr and radiograph of the involved site. The result of the culture was mainly determined from intra-operative specimen. All patients were impregnated with home-made antibiotic cement after thorough debridement of the necrotic tissue and sequestrum. The cement used in this study was Palacos®. Antibiotics used for mixing into the cement were chosen from the result of bacterial sensitivity tests. Four gram of each antibiotic were mixed with the cement powder before being poured into a mould to produce spherical beads. The number of beads impregnated into the lesion depended on the volume of dead space. The wound was closed after impregnation with antibiotic beads without inserting any drain. Oral antibiotics were given after surgery for 6-8 weeks. The results of treatment were graded at the final visit as good, fair or poor. A good result

is taken as complete resolution of the infection without recurrence, complications or functional impairment. A fair outcome presents with minimal functional impairment and complications but no recurrence. A poor result is obtained when there is no response to treatment, there is recurrence and/or major functional impairment.

RESULTS

The ages of the study population ranged between 11 and 47. Thirteen were males. Twelve patients had a previous open fracture. The most common site of involvement was the femur. Four patients had previously been impregnated with Septopal®. Underlying diseases that compromised the host immune response were found in three patients; two with diabetes and one with malnutrition. Most of the patients were type III according to the Cierny-Mader classification. Half of the patients showed leucocytosis, while about 80 percent had elevated ESR. MRSA was the commonest organism encountered (8 cases) (Table 1). Fosfomycin beads were impregnated in 5 patients and vancomycin in 4 patients. The other types of bead were ceftazidime, amikacin, cefazolin and ampicillin. The duration of bead impregnation ranged from 4 to 8 weeks. No parenteral antibiotics were administered to all patients in this series. Surgical treatment was performed to eradicate infection, ensure stabilization and augment healing in most cases. The mean hospital stay was 41 days (range 10 to 110). The number of admissions ranged from 2 to 5. A good result was achieved in 10 patients. Control of infection was achieved in all but one patient. Most of the complications encountered were related to the severity of the open fracture and prolonged immobilization. None of the cases had systemic side effect from the antibioticadministered (Table 2).

DISCUSSION

Combined local and oral antibiotic treatment was found to be effective for treating chronic osteomyelitis caused by organisms that are resistant to gentamicin. Infection was controlled in all but one patient by the last visit. There was no systemic side effect from antibiotic therapy.

Chronic osteomyelitis caused by resistant strains, especially MRSA, were more resistant and had less satisfactory outcomes compared to those caused by non-resistant strains. Sheftel et al[5] reported 5 cases of MRSA osteomyelitis treated by parenteral vancomycin. He found that 2 patients had persistant infection with one patient having renal toxicity. Ozaki et al[7] reported 2 successful results of vancomycin impregnated cement in infected prostheses caused by MRSA. In this study we showed good infection control in all but one case by using combined local antibiotic cement with oral antibiotic. The choice of antibiotic used to incorporate with the cement depended on the sensitivity of the organisms. In the case of an MRSA infection, if the organism was sensitive to fosfomycin, fosfomycin was used rather than vancomycin because of the lower price and the fewer systemic side effects that could arise. No parenteral antibiotics were used in this study. The oral antibiotics were given after the operation. The duration of oral antibiotic used was determined by the level of ESR. It is usually given for a period of 2 to 3 months. Two patients received oral antibiotics for one year because both of them had a systemic type of meliodosis, which needed prolonged antibiotic use to prevent recurrence. The duration of local antibiotic cement impregnantion was 6 to 8 weeks (Figs 1-5). Our *in vitro* study conducted earlier showed that the inhibitive effect of home-made antibiotic beads lasted about 6 weeks. One patient did not obtain control of the infection after one year of treatment. This might be associated with the prolonged course of the disease before treatment was started.

Four patients in this study had been treated with Septopal® from other hospitals. Although Septopal® has been claimed to be efficacious against most common orthopaedic infections, this study indicated that it cannot inhibit MRSA organisms[12,13]. All the antibiotics that can be used with polymethylmethacrylate were heat stable. Fusidin and rifampicin were given to patients having MRSA osteomyelitis after impregnation with beads because of their synergistic effects against this organism[14]. Palacos was chosen to mix with the antibiotic because its elution property was better than other types of cement[15].

Hospital stay of the patients in this study was shorter than in the Sheftel study[5] because no systemic antibiotics were needed. This decreased the cost and risk of secondary bacterial infection.

Fair and poor result of the treatment occurred in patients who had complications from either prolonged course of the disease or from the treatment. However, all but one patient had control of infection at the final follow-up visit.

We could not compare the efficacy of each type of antibiotic cement due to the small number of cases in our study population. There was no systemic side effect from the antibiotics used in this study. This might be explained by the low systemic absorption of the antibiotic beads.

Our limitation was the number of cases. The disadvantages of local antibiotic cement include the need for surgical removal, the possible compromise of the local immune response, and the risk of colonisation[16]. Biodegradable materials such as hydroxyapatite, chitosan and alginate are under investigation as potential carriers as an alternative to polymethylmethocrylate[17-20]. In conclusion, we have shown that combined local and oral antibiotic treatment is effective in treating chronic osteomyelitis caused by organisms resistant to gentamicin.

Table 1. Clinical data

ID	Age	Sex	Site	Causation	Under-lying disease	Previous Treatment	Associated condition	Type (C-M)	Duration	WBC	ESR	Culture
1	12	F	Tibia	Open fracture	None	None	None	IIIa	6 mth	9,700	69	Enterococci
2	19	M	Tibia	Open fracture	None	Septopal	None	IIIa	3 mth	6,800	1	MRSA
3	28	M	Tibia	Meliodosis septicemia	DM	None	Septic ankle pneumonia	IVb	1 mth	5,200	120	P. pseudomallei
4	45	M	Tibia	Open fracture	None	Plating	Fracture femur	IIIa	3 yr	7,900	58	MRSA, K. pneumonia
5	11	M	Femur	None	Malnutrition	None	Septicemia, septic knee ankle	IVb	3 yr	10,800	21	β - 1 streptococcal gr A
6	17	M	Tibia	Open fracture	None	Plating	None	IIIa	3 mth	11,500	31	P. aeruginosa
7	21	M	Femur Tibia	Open fracture	None	External Fixator	BPI	IIIa	1 yr	6,400	98	MRSA, P. aeruginosa
8	15	M	Femur	Open fracture	None	Septopal	Hip dislocation	IIIa	3 mth	6,000	32	MRSA
9	36	M	Femur	Open fracture	Hyperthyroidism	Plating	None	IVa	3 yr	6,400	20	Enterococci, MRSA
10	47	M	Tibia	Melliodosis septicemia	DM, gout Hyperthyroidism	None	Septicemia respiratory failure	IVb	3 mth	11,700	135	P. pseudomallei
11	44	M	Femur	Open fracture	None	Plating	None	IIIa	3 mth	23,800	88	MRSA
12	22	F	Pelvis	Open fracture	None	Wiring	None	IVa	2 yr	19,100	71	Enterococci
13	22	M	Femur	Open fracture	None	None	None	IIIa	3 mth	10,100	40	MRSA
14	31	M	Femur	Open fracture	Asthma	None	None	IIIa	1 mth	10,900	30	MRSA
15	30	M	Femur	Open fracture	None	Plating	None	IIIa	1 mth	7,800	30	P.aeruginosa

C-M = Cierney-Mader classification

BPI = Brachial plexus injury

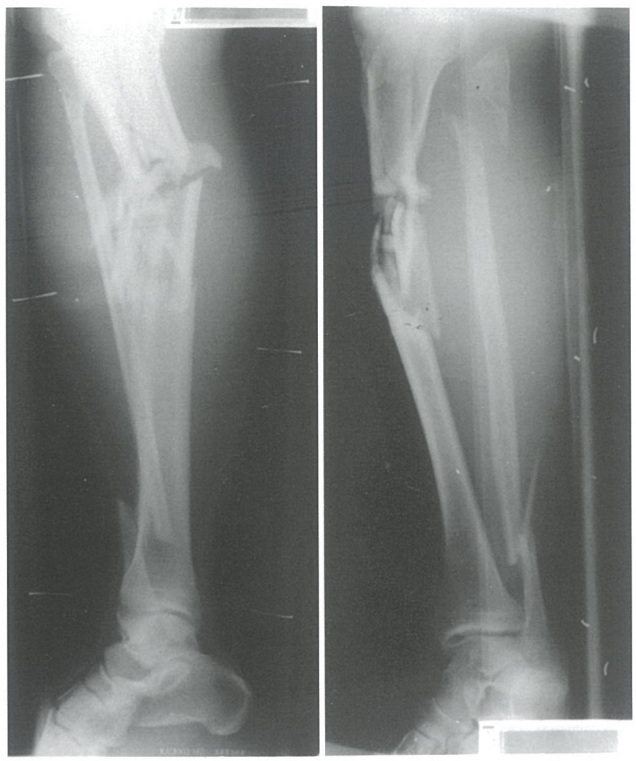
MRSA = Methicillin-resistant *Staphylococcus aureus*

Table 2. Treatment and result

	Oral antibiotic	Type of bead	Duration of bead	Surgery	Number of admissions	Hospital stay (days)	Result	Follow-up	Complications
1	Rifampicin + fusidin	Fosfomycin	8 wk	Sequestrectomy	2	19	Good	3 yr	None
2	Rifampicin + fusidin	Vancomycin	8 wk	Flap + grafting	2	26	Good	1 yr	None
3	Augmentin + doxycyclin	Ceftazidime	6 wk	Grafting	2	10	Fair	1 yr 6 mth	Stiff ankle
4	Rifampicin fusidin	Fosfomycin	12 wk	Grafting, off plate	3	27	Fair	1 yr 6 mth	LLD, stiff knee
5	Cephalexin	Cefazolin	8 wk	Sequestrectomy	2	16	Good	3 yr	None
6	Ciprofoxacin	Ciprofoxacin	6 wk	Off plate, grafting	2	15	Good	1 yr	None
7	Ciprofoxacin + rifampicin fusidin	Fosfomycin+ ceftazidime	8 wk	Flap, grafting	2	45	Fair	1 yr	Stiff knee
8	Rifampicin + fusidin	Vancomycin	8 wk	External fixator	5	65	Fair	5 yr	Recurrence infection
9	Rifampicin + fusidin	Fosfomycin	6 wk	Sequestrectomy	5	60	Poor	1 yr	Persistent infection
10	Ciprofoxacin	Ceftazidime sequestrectomy	6 wk	Synovectomy,	3	34	Good	1 yr 6 mth	None
11	Rifampiciin + fusidin	Fosfomycin	6 wk	External fixator, grafting, quadriceplasty	3	27	Good	7 yr	None
12	Amoxycillin	Ampicillin	8 wk	Off wiring	2	15	Good	7 yr	None
13	Rifampicin + fusidin	Vancomycin	8 wk	Grafting	3	59	Good	7 yr	None
14	Rifampicin + fusidin	Vancomycin	8 wk	STSG	3	43	Good	6 yr	None
15	Ciprofoxacin	Ciprofoxacin	7 wk	Off plating	3	35	Good	4 yr	None

LLD = Leg-length discrepancy

STSG = Split thickness skin graft



Figs. 1a, b. Radiographs of Case 4 showing severe comminuted fracture of proximal tibia type IIIA.

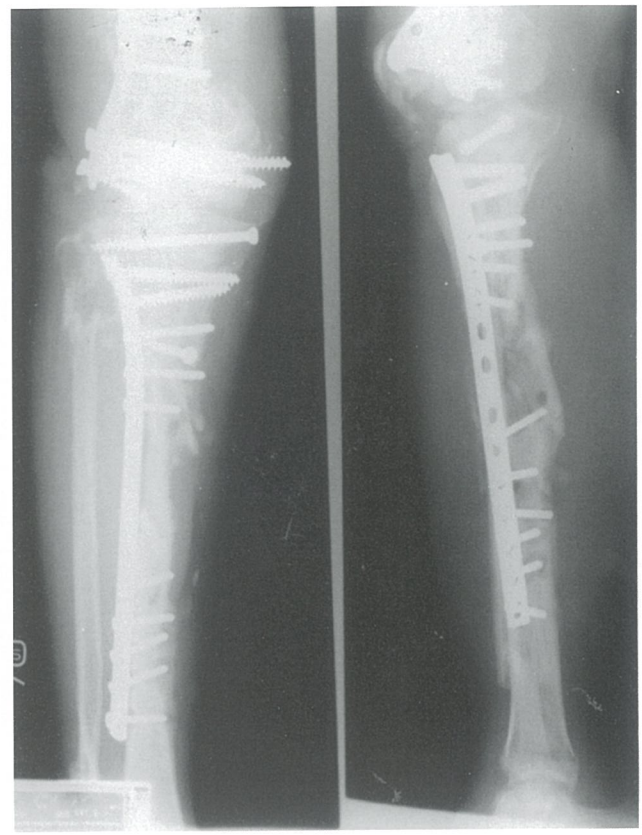


Fig. 2. Six months after plating from nearby hospital. The patient was referred to our hospital with chronic osteomyelitis of tibia and plate loosening.

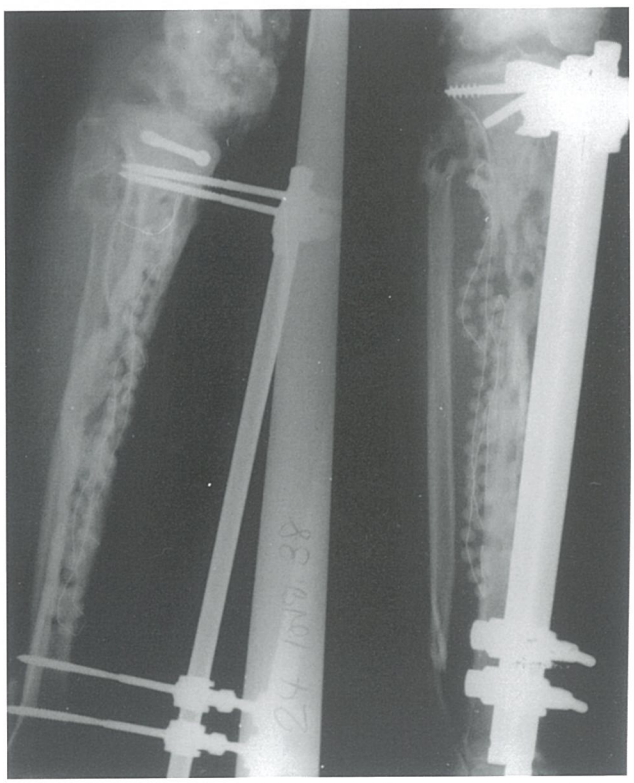


Fig. 3. After removal of the plate, locally made fosfomycin bead and external fixator were applied.

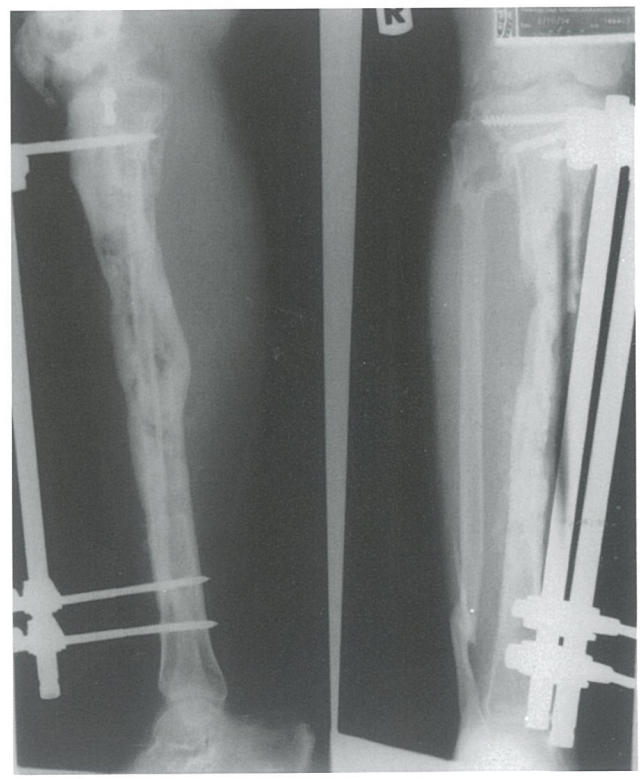


Fig. 4. Bone grafting was performed to fill the defect after removal of the beads.

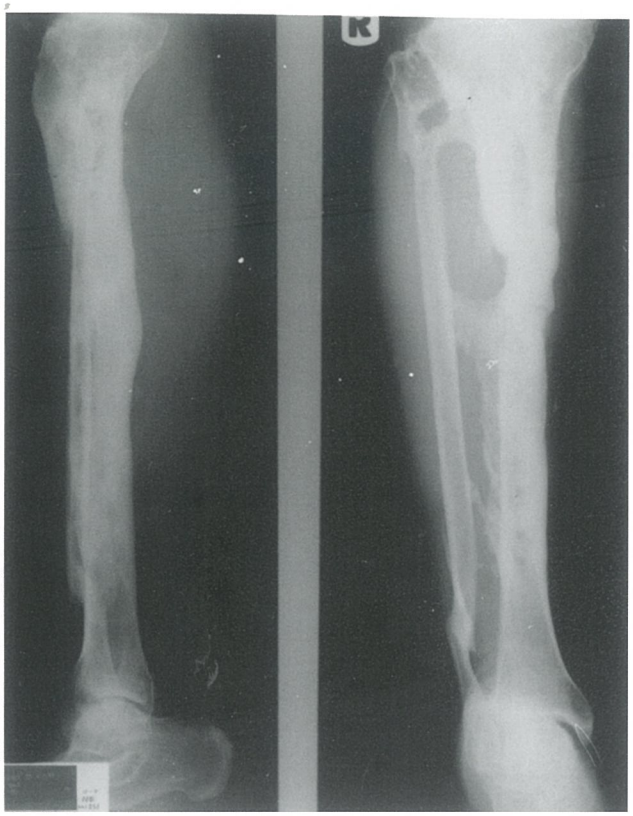


Fig. 5. One-year follow-up radiograph showing consolidation of graft and arrest of infection.

REFERENCES

1. Mulligan E, Marray-Leisure KA, Standiford HC, et al. Methicillin-resistant Staphylococcus aureus: a consensus review of the microbiology, pathogenesis and epidemiology with implications for prevention and management. Am J Med 1993;94: 313-326.
2. Musher DM. The gram-positive cocci: III, resistance to antibiotic. Hosp Pract 1988;23:105.
3. Craven DE, Reed C, Kollisch N, et al. A large outbreak of infections caused by strain of Staphylococcus aureus resistant to oxacillin and aminoglycosides. Am J Med 1981;71:53.
4. Watanakaukorn C. Treatment of infection due to methicillin-resistant Staphylococcus aureus osteomyelitis in a neonate. JAMA 1981;245:1662.
5. Sheftel T, Mader JT, Pennick JT, Cierny III G. Methicillin-resistant Staphylococcus aureus osteomyelitis. Clin Orthop 1985;198:231-239.
6. Waldvogel FA, Vase H. Osteomyelitis: the post decade. N Engl J Med 1980;303:360
7. Ozaki T, Yoshitaka T, Kunisada T, et al. Vancomycin impregnated polymethylmethacrylate beads for methicillin-resistant Staphylococcus aureus (MRSA) infection: report of two cases. J Orthop Sci 1998;3(3):163-168.
8. Sorrell TC, Packham DR, Shanker, et al. Vancomycin therapy for methicillin-resistant Staphylococcus aureus. Ann Intern Med 1982;97:344.
9. Mader JT, Shirtliff ME, Berquist SC, Calhoun J. Antimicrobial treatment of chronic osteomyelitis. Clin Orthop 1999;390:45-65.
10. Blaha JD, Nelson CL, Frevert LF, et al. The use of Septopal (polymethylmethacrylate beads with gentamicin) in the treatment of chronic osteomy elitis. Instruct Course Lect. AAOS 1990;509-514.
11. Klemm KW. Antibiotic bead chains. Clin Orthop 1993;295:63-76.
12. Buranapanitkit B, Wongsiri S, Ingviya N, et al. In vitro elution characteristic of antibiotic cement on MRSA organism. J ASEAN Orthop Ass 2000;295:
13. Buranapanitkit B, Wongsiri S, MRSA (Methicillin-resistant Staphylococcus aureus) osteomyelitis: factors and results compared to non MRSA osteomyelitis. J ASEAN Orthop Ass 2000;13(1):53-54.
14. Drancourt M, Stein A, Argenson JN, et al. Oral treatment of staphylococcus spp-infected orthopaedic implants with fusidic acid or ofloxacin in combination with rifampicin J Antimicrob Chemother 1997;39:235-240.
15. Calhoun JH, Mader JT. Antibiotic beads in the management of surgical infection. Am J Surg 1989;157:443-449.
16. Petty W. The effect of methylmethacrylate on bacterial phagocytosis and killing by human polymorphonuclear leucocytes. J Bone Joint Surg 1978;60A:752-757.
17. Calhoun JH, Mader JT. Treatment of osteomyelitis with a biodegradable antibiotic implant. Clin Orthop 1997;341:206-214.
18. Shinto Y, Uchida A, Korkusaz F, et al. Calcium hydroxyapatite ceramic used as a drug delivery system for antibiotics. J Bone Joint Surg 1992;74B:600 604.
19. Aimin C, Chunlin H, Juliang B, et al. Antibiotic loaded chitosan : an in vitro, in vivo study of a possible treatment for osteomyelitis. Clin Orthop 1999;366:239-247.
20. Lin SS, Ueng SWN, Liu SJ, et al. Development of a biodegradable antibiotic delivery system 1999;362:240-250.