Antibiotic treatment for bone infection after debridement: 2 weeks or 6 weeks?

Xiaohua Wang (wangxiaohua29@163.com)
Southwest Hospital
Li Fang
Southwest Hospital
Shulin Wang
Southwest Hospital
Huan Ma
Southwest Hospital
Hongwen Zhao
Southwest Hospital
Zhao Xie
Southwest Hospital

Research article

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Abstract

Purpose: Our aim was to investigate the clinical efficacy and complications of antibiotics treatment duration for the patients of bone infection.

Methods: We retrospectively analyzed the patients with bone infection admitted to our hospital between March 2013 and October 2018. The surgical debridement was performed and the patients were divided into three groups: IV group (Intravenous antibiotics for 2 weeks); Oral group (Intravenous antibiotics for 2 weeks followed by oral antibiotics for 4 weeks); Rifampicin group (Intravenous antibiotics for 2 weeks followed by oral antibiotics plus rifampicin for 4 weeks). The infection control rate and complications were compared.

Results A total of 902 patients were enrolled, the infection sites included 509 tibias, 228 femurs, 32 humeri, 23 radii and ulnae, 40 calcanei, 23 multiple-site infections and the other sites 47 cases. After at least 6 months of follow-up, 148 (16.4%) patients had recurrence of infection. The recurrence rate of IV group was 17.9%, which was no significant higher than that of Oral group (10.1%) or Rifampicin group (10.5%). The abnormal rate of Glutamic-pyruvic transaminase(ALT) in IV group was 15.1%, which was lower than that of Oral group (18.0%) and Rifampicin group (27.4%), P=0.026. The positive rates of proteinuria in the three groups were 3.2%, 4.5%, and 9.3%, respectively, P=0.020.

Conclusion: After debridement of bone infection, the additional oral antibiotic treatment may increase the damage of liver and kidney, and can not significantly reduce the infection recurrence rate. Therefore, it is recommended to adopt short-term systemic antibiotic treatment after debridement.

Introduction

Bone infection is a common complication after bone fracture and often with poor curative effect, although the advancement of various theories and techniques has brought the treatment to a new height, it is still one of the most difficult diseases for orthopedics. The commonly used methods include conservative debridement, continue flushing, antibiotic carrier filling and others, the clinical effects vary widely. In order to achieve good results, previous clinicians often use antibiotic therapy that is parenteral, high dose, and prolonged [1], but intravenous therapy carries with it substantial risks and inconvenience to patients[2], at the same time, long-term intravenous antibiotics therapy may bring the complication of catheter-related bloodstream infection and thrombosis[3]. At present, the mainstream treatment method is debridement followed by systemic antibiotics therapy, commonly intravenous infusion for 2 weeks followed by oral antibiotics for 4–6 weeks[4, 5]. But there is no evidence that antibiotics therapy for 4–6 weeks improves outcomes compared with shorter regimens[1], at the same time, long-term application of antibiotics may lead to adverse reactions to liver and kidney [6], so whether it is necessary to follow the traditional antibiotic treatment strategy after debridement, the answer is confused. We explored the use of debridement combined with short-term antibiotics in the treatment of bone infection, aimed to observe

the clinical efficacy and complications, provide a reference for systemic antibiotics application for bone infection.

Patients And Methods

After receiving approval from our Institutional Review Board, we retrospectively analyzed the patients with bone infection admitted to our hospital between March 2013 and October 2018. The inclusion criteria were: Patients with bone infection; Treatment with debridement, filled with antibiotic cements; Systemic antibiotics were used postoperatively. The exclusion criteria were: Diabetic foot infection; Patients without surgical treatment; Those with autoimmune disease and having generalized vascular insufficiency; Patients with incomplete follow-up data, Liver and kidney dysfunction preoperatively; Bone graft performed within 6 months after the debridement. The study flow chart showed in Fig. 1.

Treatment methods

In those patients, debridement and implanted with antibiotic cements were performed, remove the cements after infection was eradicated and to repair the bone defects. In this study, only the infection control process was involved, do not evaluate the process of bone defect repair. In the operation, sequestrum and necrotic tissue were removed to identify the bacteria and drug susceptibility test. After debridement, bone defects were filled with antibiotic PMMA cement (Heraeus, Germany). Different fixing methods (plate internal fixation, plate external fixation, no fixation) were used according to the cinery-mader classification, and negative pressure drainage was left for 10 to 12 days.

The patients were divided into three groups according to whether oral antibiotics were taken after surgery. IV group (Intravenous antibiotics for 2 weeks); Oral group (Intravenous antibiotics for 2 weeks followed by oral antibiotics for 4 weeks); Rifampicin group (Intravenous antibiotics for 2 weeks followed by oral antibiotics plus rifampicin for 4 weeks). There was no significant statistical difference in the general data: fixing methods; cierny-mader classifications; bacteria, etc. The bacteria and their antibiotics we used were shown in Table 1.

Postoperative management and follow-up

All the patients were examined for liver and kidney function and urine routine on the 1st, 7th, and 14th day after surgery, after that, take the same examination weekly for the oral group and rifampicin group, and urine protein was repeatly examinated at the 6th week. Infection control and recurrence criteria [6]: Apparent cure was defined as the absence of signs or symptoms of osteomyelitis for at least 6 months after cessation of antimicrobial therapy. Relapse was defined as infection occurring at the same site from which it was apparently eliminated, requiring specific treatment with antibiotics or surgery. ALT and AST value greater than 40 U/L and Cr value greater than 104 umol/L was defined as abnormality.
The relevant comparison of measurement data (recurrent time) using one-way analysis of variance or rank sum test. Comparison of the enumeration data (The abnormal rate of ALT, AST and Cr, proteinuria,

infection control rate) using the Pearson's chi-square test. P value below 0.05 was considered as significant.

Results

A total of 902 patients were enrolled in this study, there were 717 males and 185 females with an average age of 40.25 (4–76) years, the mean duration of infection before admitted to our hospital was 70.7 months (14 days to 720 months). The infection sites included 509 tibias, 228 femurs, 32 humeri, 23 radii and ulnae, 40 calcanei, 23 multiple-site infections and the other sites 47 cases. There were 666 cases of post-traumatic infection and 236 with hematogenous osteomyelitis. 640 (71%) patients with positive bacteria isolated. Of these, 307 (48.0%) were infected with Staphylococcus aureus (including 81 MRSA), 56 (8.8%) with pseudomonas aeruginosa, 41(6.4%) with Escherichia coli, 33 (5.2%) with Enterobacter cloaca, 39 (6.0%) with staphylococcus epidermidis, 25 (3.9%) with klebsiella pneumoniae, 64 (10%) with other bacteria, 75(11.7%) isolated with two or more bacteria, and the remaining 262 cases were negative.

There were 148 (16.4%) recurrence of infection with at least 6 months of follow-up, with an average recurrence time of 63.0 ± 4.8 (4-176) days. The recurrence rate of IV group was 17.9%(130/727), which was no significant higher than that of Oral group and Rifampicin group, respectively 10.1%(9/89)and 10.5%(9/86), P = 0.051. The recurrence time of the three groups was 62.37 ± 6.93, 58.56 ± 13.44, 76.33 ± 17.48 days respectively, P = 0.851. There were 727 patients in IV group, of which 130 patients relapsed, the highest recurrence rate bacteria was P. aeruginosa, which with a recurrence rate of 40.4% (19/47), and the recurrence rate of patients with negative bacterial isolated was 8.1% (19/236), P < 0.01.

The abnormal rate of ALT in IV group was 15.1%, which was lower than that of oral group (18.0%) and rifampicin group (27.4%), P = 0.026. The positive rates of proteinuria in the three groups were 3.2%, 4.5%, and 9.3%, respectively. P = 0.020. There was no significant statistical difference in the abnormal rate of AST (P = 0.798) and Cr (P = 0.620) among the three groups.

Discussions

Treatment of bone infection has been tricky. At present, the overall treatment strategy includes conservative treatment, palliative debridement, En-block resection and amputation, but there has been a lack of uniform treatment standards. Operation is easily accepted by clinicians, but not all cases require surgical debridement[1], many infectious disease can be effectively treated with oral therapy[7–9]. Hamed[10] reported that intravenous antibiotics (6 weeks) and oral suppression therapy were administered for cases of PJI infection, with reliable clinical efficacy. Research showed that drug therapy alone had an average success rate of 71.1%, surgical treatment alone had an average of 88.9% [11]. Systemic intravenous antibiotics after debridement can achieve a rapid reduction of the bacterial load at the site of infection [12]. Therefore, the industry is more inclined to surgical treatment combined with antibiotic treatment, which is beneficial to arrest the infection.

Study pointed out that the treatment of acute hematogenous osteomyelitis is intravenous antibiotics for several weeks, and then converted into oral antibiotics until symptoms and signs are alleviated [13, 14], but for chronic bone infection, debridement is often the first chose. Although research showed[1] that oral and parenteral therapies achieve similar cure rates, clinicians accustomed to consider of intravenous antibiotics [15, 16], then converted to oral antibiotics. Reported that intravenous antibiotics for less than one week have no significant effect on prognosis [17–19]. We applied debridement plus systemic antibiotics treatment, most patients (80.6%)use intravenous antibiotics only for 2 weeks, although long-term antibiotic use has achieved good results in previous reports, our results showed the recurrence rate of IV group was not significantly different from the other two groups and the overall infection control rate was 83.6%, the infection control rate is comparable to previous reports, which support the applied of short-term systemic antibiotic treatment after debridement.

Multiple and refractory bacterial is common for bone infection, especially for those with chronic infection, so combined antibiotics treatment are commonly applied in the clinics. The most common oral combination drug is rifampicin, which have bactericidal effect to multiple Gram-positive and negative bacteria [16], it can achieves high intracellular levels and capable of penetrating bacterial biofilm [20, 21]. However, it is not advisable applied anti-infection alone, because it can cause resistance quickly[5], rifampicin should be started after an bacterial load reduction by surgery and the wound is dry[22, 23]. In this study, 307 (48.0%) patients were infected with Staphylococcus aureus and 56 (8.8%) with pseudomonas aeruginosa, accounts for more than 50% of the isolated bacteria, so levofloxacin was more applied in our clinics. Reported that levofloxacin alone was unable to eradicate methicillin-susceptible S. aureus[24, 25], for the bone infection caused by Staphylococcus aureus and P.aeruginosa, the classic antibiotic combination is levofloxacin plus rifampicin.

How long does it take for infection to be cleared after treatment of bone infection? There is no answer. Urania Rappo[26] evaluated the efficacy of infection after 6 weeks treatment. Daver NG[6] indicated that the infection apparent cure when it does not recur in 6 months. We evaluated infection control at 6 months after operation, which may miss some recurrence cases, but the missing cases is less, because our statistics show that most cases have a recurrence time within 2 months.

Rifampicin is rarely used alone in the treatment of bone infections, but its combination with other antibiotics can increase the treatment outcomes of other antibiotics, it diffuses very well within bone tissue and bacterial biofilms [27], but Rifampicin often elicits a hepatotoxic response and gastroenteropathy. Our results indicated that the ALT abnormal rate of rifampicin group is the highest, suggesting that postoperative combination may lead to liver damage. At the same time, Sahoko[28] reported that rifampicin can cause acute renal damage, our results showed that the overall complication was acceptable in the three groups, the recurrence rate of IV group was not significantly different from the other two groups, while the oral group and rifampicin group had higher ALT and proteinuria positive rate, the abnormality may caused by the additional oral therapies. Although the proteinuria of the rifampicin group was the highest, the creatinine positive rate was not statistically significant difference, suggesting that the additional rifampicin therapies may cause early or mild renal damage.

Although there are many highlights in this article, the sample size is large, it used standard techniques. However there are several drawbacks. First, the bacteria, fixation methods and many heterogeneous patients may affect the results. Second, the abnormality of ALT and urinary protein suggested the possible damage of liver and renal, but can not determine the extent of the damage. Third, bone infection is a disease that is easy to recurrence, this study with short-term (6 months) follow-up, the long-term recurrence rate for those patients is still inconclusive.

Conclusions:

After debridement of bone infection, the overall efficacy of 2 weeks antibiotics treatment is reliable. The additional oral antibiotic treatment may increase the damage of liver and kidney, and can not significantly reduce the infection recurrence rate. Therefore, it is recommended to adopt short-term systemic antibiotic treatment after debridement.

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Tables

Table.1 The bacteria and the antibiotics we used

Bacteria	Intravenous antibiotics	Oral antibiotics
MSSA/MSSE	First or second generation cephalosporins/ Fluoroquinolones (Levofloxacin, Moxifloxacin)	Fluoroquinolones/First and second generation cephalosporins for children
MRSA/MRSE	Vancomycin/Linezolid	Linezolid/ Fluoroquinolone/Minocycline
P.aeruginosa/E.coli/E.cloaca/K. pneumoniae	Ceftazidime/Cefepime/Piperacillin tazobactam/ Levofloxacin/Amikacin (usually used in combination)	Levofloxacin
Others	According to drug sensitivity	According to drug sensitivity
Negative	Ceftazidime / Cefepime / Fluoroquinolone	Levofloxacin

MSSA/MSSE: Methicillin-susceptible *Staphylococcus aureus/ epidermidis*

e.2 Comparisons of general information, clinical efficacy of the three groups

ts	IV group	Oral group	Rifampicin group	P Value
ber	727	89	86	-
atio (male/female)	3.9 (578/149)	4.6 (73/16)	3.3 (66/20)	0.688
age age(years)	37.11±1.62	40.30±3.22	38.91±2.54	0.130
age duration of infection(months)	70.3±6.5	68.1±11.8	75.9±8.1	0.255
of infection (posttraumatic/hematologic)	541/186	67/22	58/28	0.360
rrence rate of infection	17.9%130/727	10.1%9/89	10.5%9/86	0.051
rrence time(days)	62.37±6.93	58.56±13.44	76.33±17.48	0.851
rmal rate of ALT	15.1%110/727	18.0%16/89	27.9%24/86	**0.026**
rmal rate of AST	16.4%119/727	14.6%13/89	13.9%12/86	0.798
rmal rate of Cr	1.1%8/727	1.1%1/89	2.3%2/86	0.620
ive rates of proteinuria	3.2%23/727	4.5%4/89	9.3%8/86	**0.020**

: White blood cell; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate

Declarations

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Conflict of interest statement

We declare that there is no conflict of interest with any institution

Ethical review committee statement

The Ethics Committee of the first affiliated hospital of Army Medical University, PLA approved all protocols.

Figures

Figure 1

study flow chart