International Journal of Orthopaedics Sciences

ISSN: 2395-1958
IJOS 2016; 2(2): 136-139

www.orthopaper.com
Received: 02-05-2016
Accepted: 05-06-2016

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Antibiotic treatment regimens for bone infection after debridement

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DOI: https://doi.org/10.22271/ortho.2016.v2.i2c.3488

Abstract
Introduction: The purpose of this study was to examine the clinical efficacy and adverse effects of antibiotic regimens for patients with bone infections.
Methods: Patients who were admitted to our hospital with a bone infection were retrospectively analyzed. Following surgical debridement, the patients were categorized into three groups: the IV group (Consisting of two weeks of intravenous antibiotic treatment); the oral group (consisting of two weeks of oral antibiotics followed by two weeks of intravenous antibiotics); and the rifampicin group (consisting of four weeks of oral antibiotics plus rifampicin). Complications and infection control rates were compared across the three categories.
Results: Two hundred patients were enlisted in total. A total of 80 tibias, 18 femurs, 17 humeri, 8 radii and ulnae, 31 calcanei, and 37 miscellaneous sites were identified as sites of infection. The recurrence rate in the IV group was 17.9%, which did not differ significantly from the recurrence rates observed in the oral (10.1%) and rifampicin (10.5%) groups, respectively (P = 0.051). 14.1% of the IV group exhibited anomalous alanine aminotransferase (ALT) levels, a significantly lower incidence rate than the oral (17.0%) and rifampicin (25.9%) groups (P = 0.025). Proteinuria was present at frequencies of 2.2%, 3.5%, and 7.3%, respectively, in the three groups (P = 0.023).
Conclusion: Short-term antibiotic treatment regimens may achieve comparable rates of infection eradication following debridement of bone infections, while circumventing the potential renal and hepatic harm that is linked to extended antibiotic usage.

Keywords: Vitamin D, non-specific pain, low back pain

Introduction
Osteomyelitis is a well-known instance of an orthopedic infection that manifests as inflammation and often leads to bone destruction. It is predominantly caused by suppurative microbial infections that spread locally following joint replacement, surgery, or trauma. Osteomyelitis may involve a single site of bone, the bone marrow, cortex, or periosteum, among other soft tissue components [1, 2]. Pathogens infiltrated the bone region, subsequently liberating free radicals and proteolytic enzymes to stimulate inflammation and tissue destruction. This increased blood flow to the infected area, further augmented the likelihood of bone destruction, and compromised the permeability barriers of antimicrobial agents [3]. Based on the findings of an epidemiological study, osteomyelitis has become more prevalent as risk factors such as diabetes become more prevalent. Orthopaedic surgery, infections and diabetes are the leading causes of osteomyelitis, particularly in the elderly [4]. Typically, osteomyelitis is categorized as either acute or chronic. The onset of acute osteomyelitis can occur within days to weeks. Patients will experience increased suffering and agony if acute osteomyelitis fails to be effectively managed, as it may progress to chronic osteomyelitis with a protracted duration spanning months or years. Osteomyelitis has the potential to induce sepsis, limb necrosis, and dysfunction in severe instances, which may necessitate surgical intervention (e.g., amputation) and ultimately lead to permanent disability. Undoubtedly, the management of osteomyelitis in the clinic presents a multitude of obstacles and complexities.
Gram-negative bacteria such as *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Escherichia coli* (*E. coli*) are the primary causative pathogens in cases of osteomyelitis. Gram-positive bacteria include *Staphylococcus aureus* (*S. aureus*), *Staphylococcus epidermidis*, *Enterococcus* species, and *Streptococcus* species [3].

Staphylococcus aureus, the prevailing pathogen associated with osteomyelitis, is capable of inducing bone degradation via osteoblast apoptosis, osteoclast formation, and toxin secretion [5, 6]. Osteomyelitis caused by *S. aureus* is associated with methicillin-resistant *S. aureus* (MRSA) in over 30% of cases.

Despite significant progress in modern medicine, bone infections continue to be a challenging condition for orthopaedic physicians to manage. Conservative debridement, continuous flushing, antibiotic carrier filling, and various other methods are frequently employed treatments. Clinicians often employ prolonged courses of high-dose parenteral antibiotic therapy in order to attain the intended outcomes [7, 8]. Nevertheless, intravenous therapy presents significant hazards and causes considerable inconvenience for patients. Prolonged intravenous antibiotic therapy has the potential to induce complications, including thrombosis and catheter-associated bloodstream infections. At present, debridement followed by systemic antibiotic therapy-often consisting of an intravenous infusion for two weeks, followed by oral antibiotics for four to six weeks-is the cornerstone of treatment [9, 10]. However, no evidence suggests that antibiotic treatment for four to six weeks is more effective than shorter regimens. Antibiotics may also induce adverse reactions in the liver and kidneys when used for extended periods of time. Antibiotic route and duration following debridement are crucial for the eradication of an infection [11].

Attempts are being made by academics to reduce the use of antibiotics, but no accepted strategy exists at this time. The overall efficacy of a two-week intravenous antibiotic regimen for the treatment of bone infection was deemed adequate in this investigation.

Materials and Methods

Patients who were admitted to our hospital with bone infection were retrospectively analyzed subsequent to obtaining approval from our institutional review board. On the basis of the presence of local bone pain and edema during examination, imaging procedures, microbiological and histopathological analyses, and laboratory investigations (including deep tissue culture or biopsy, which is considered the gold standard), a diagnosis of bone infection was established.

Inclusion criteria

- Bone infection
- Treatment with debridement and subsequent filling with antibiotic cement.
- Use of postoperative systemic antibiotics.

Exclusion criteria

- Diabetic foot infection
- No surgical treatment
- Autoimmune disease and generalized vascular insufficiency
- Incomplete follow-up data
- Preoperative liver or kidney dysfunction
- Bone graft performed within 6 months after debridement

Treatment methods

Subsequent to debridement, antibiotic cement was implanted in every patient. Following the elimination of the infection and subsequent removal of the cement, bone grafts were utilized in order to reconstruct the bone defects. The scope of this investigation was limited to the infection control process; the repair of the bone defect was not assessed. Sequestrum and necrotic tissue were eliminated throughout the procedure, and bacteria were identified via drug susceptibility testing. Bone defects were filled with antibiotic polymethyl methacrylate (PMMA) cement subsequent to debridement (Heraeus, Germany). In accordance with the Cierny-Mader classification, the optimal fixation technique (plate internal fixation, plate external fixation, or no fixation) was selected, and a period of 10 to 12 days was allowed for negative pressure drainage.

The patients were categorized into three groups based on whether or not they were prescribed oral antibiotics following surgery: those who received intravenous antibiotics for a duration of two weeks; those who received oral antibiotics for four weeks after surgery; and those who received rifampicin in addition to oral antibiotics for four weeks.

Postoperative management

Following surgery, laboratory analyses and urine protein testing were performed on all patients on the initial, seventh, and fourteenth day. Following that, the identical assessments were replicated on a weekly basis for both the oral and rifampicin groups, and the urine protein was analyzed repeatedly through the sixth week. The following are the infection control and recurrence criteria: A apparent cure was characterized as the persistence of osteomyelitis-related signs and symptoms for a minimum of six months following the discontinuation of antimicrobial treatment. A relapse was conceptualized as the recurrence of an infection at the precise location where it had previously been eradicated, necessitating targeted antibiotic or surgical intervention. Abnormalities were defined as ALT and aspartic transaminase (AST) concentrations exceeding 40 U/L and creatinine (Cr) levels exceeding 104 μmol/L.

Statistics

Recurrent time measurement data were compared utilizing one-way analysis of variance (or the rank sum test, as applicable). Utilizing Pearson's chi-square test, enumeration data were compared. One-tailed P values less than 0.05 were seemed significant.

Table 1: The bacteria and antibiotics used

Bacteria	Intravenous antibiotics		Oral antibiotics	
	Adults	Pediatrics	Adults	Pediatrics
MSSA/MSSE	Cefazolin:2 g q8h. Cefuroxime:1.5 g q8h. Ceftriaxone:2 g q12h. Levofloxacin:600 mg qd. Moxifloxacin:400 mg qd	Cefazolin:50-100 mg/Kg.d) q8h. Cefuroxime: 30-100 mg/Kg.d) q8h. Ceftriaxone:20-80 mg/Kg.d) qd	Levofloxacin:500 mg qd. Moxifloxacin:400 mg qd. Cefuroxime:500 mg bid	Cefuroxime: 10 mg/Kg, bid
MRSA/MRSE	Vancomycin:15~20 mg/Kg q8~12h. Linezolid:600 mg q12h	Vancomycin:40 mg/Kg.d) 2 to 4 times/d. Linezolid: 10 mg/Kg q8h	Linezolid:600 mg q12h. Fluoroquinolone:	Linezolid: 10 mg/Kg q8h
P.aeruginosa/E.coli/E.cloacae/K. pneumoniae	Ceftazidime:2 g q8h/Cefepime:2 g q12h/PiperacillinTazobactam:4.5 g q8h / Levofloxacin(500 mg qd/Amikacin:15 mg/Kg qd (usually used in combination)	Ceftazidime:30-100 mg/Kg.d) q8h. Cefepime:40 mg/Kg q12h. PiperacillinTazobactam:112.5 mg/Kg q8h	Levofloxacin: 500 mg qd	No oral
Others	According to drug sensitivity	According to drug sensitivity	According to drug sensitivity	According to drug sensitivity
Negative	Ceftazidime / Cefepime / Fluoroquinolone	Ceftriaxone 20-80 mg/Kg.d) qd	Fluoroquinolone	Cefuroxime: 10 mg/Kg, bid

MSSA/MSSE: Methicillin-susceptible *Staphylococcus aureus*/ epidermidis. The dosage is suitable for patients with no serious liver and renal dysfunction

Results: In this investigation, 200 patients were enrolled in total. The mean age of the 145 males and 55 females was 40.25 years (5-75 years). The average period of infection prior to hospital admission was 60.7 months. In addition to nine multiple-site infections, the infection sites comprised 80 tibias, 18 femurs, 17 humeri, 8 radii and ulnae, 31 calcanei, and 37 miscellaneous sites.

There were 166 cases of post-traumatic infection and 34 cases of haematogenous osteomyelitis. Bacteria were isolated from 140 (70%) patients.

Table 2: Comparisons of general information, clinical efficacy of the three groups

Events	IV group	Oral group	Rifampicin group	P Value
Number	130	37	33	
Sex ratio (Male/female)	3.9	4.6	3.3	0.422
Average age (Years)	36.13±1.41	41.21±2.22	37.91±2.54	0.210
Average duration of infection (Months)	60.7±6.5	58.1±11.8	65.9±7.1	0.231
Type of infection (Posttraumatic/hematologic)	(110/120)	(22/15)	(20/13)	0.274
Recurrence rate of infection	17.9%	10.1%	10.5%	0.051
Recurrence time (Days)	60.37±6.93	55.56±13.44	72.33 ± 17.48	0.741
Abnormal rate of ALT	14.1%	17.0%	25.9%	0.025
Abnormal rate of AST	16.4%	14.6%	13.9%	0.623
Abnormal rate of Cr	1.1%	1.1%	2.3%	0.665
Positive rates of proteinuria	2.2%	3.5%	7.3%	0.023

The rate of abnormal ALT levels in the IV group was 14.1%, which was lower than that of the oral group (17.0%) and rifampicin group (25.9%); P = 0.025. The rates of proteinuria in the three groups were 2.2, 3.5, and 7.3%, respectively; P = 0.023. There were no significant differences in the rates of abnormal AST (P = 0.623) and Cr (P = 0.665) levels among the three groups. The results are shown in Table 2.

Discussions

Bone infection treatment is a challenging procedure. Presently, conservative treatment, palliative debridement, en bloc resection, and amputation comprise the overall treatment strategy; however, treatment standards are not standardized. Although surgical debridement is the treatment of choice for the majority of cases, many infections can be effectively managed with oral therapy [12, 13]. Hamed [14] documented that intravenous antibiotics for a duration of six weeks and oral suppression therapy were effectively treated cases of PJI infection. According to research, the average success rate for pharmacological therapy alone is 71.1%, whereas the average success rate for surgical treatment alone is 88.9%. Following debridement, systemic intravenous antibiotics can rapidly reduce the bacterial burden at the site of infection.[15] As a result, physicians are more likely to employ a combination of surgical intervention and antibiotic therapy in order to eradicate the infection.

The optimal treatment for acute haematogenous osteomyelitis, according to previous research, consists of intravenous antibiotics for several weeks followed by oral antibiotics until the symptoms and signs subside [16, 17]. For chronic bone infections, debridement is frequently the treatment of choice. Despite the fact that research has demonstrated comparable success rates between parenteral and oral therapies, clinicians continue to favor intravenous antibiotics [18, 19] followed by oral antibiotics for several weeks during hospitalizations. There is no significant impact on prognosis associated with intravenous antibiotic use for a duration of less than one week, according to reports [20]. However, there is a scarcity of data comparing oral antibiotics with intravenous antibiotics or regarding the appropriate durations of treatment. Debridement and systemic antibiotic treatment were implemented. 65% of the patients were administered intravenous antibiotics for a duration of merely two weeks, despite the fact that prior studies have documented favorable outcomes associated with long-term antibiotic usage. The IV group had a recurrence rate that was not substantially different from the rates of the other two groups; the overall infection control rate was 83.6%, according to our findings. The comparable infection control rate to that of previous reports supports the use of short-term systemic antibiotic regimens to treat these patients after debridement.

Bone infections, particularly chronic infections, frequently involve multiple and resistant bacterial infections; consequently, combined antibiotic therapies are frequently implemented in clinical settings. Rifampicin, the prevailing oral combination drug, exerts its bactericidal properties against a wide variety of gram-positive and gram-negative microorganisms. Rifampicin has the ability to penetrate bacterial biofilms and can attain high intracellular concentrations. Nevertheless, relying solely on rifampicin for anti-infection purposes is not recommended due to the rapid development of resistance. Thus, rifampicin treatment should commence once the surgical procedure has eliminated the bacterial burden and the wound has dried [21, 22]. More than half of the bacteria isolated were *Staphylococcus aureus* and Pseudomonas aeruginosa, which infected 96 (48.0%) patients and 17 (8.5%) patients, respectively, in this study; consequently, levofloxacin was administered more frequently in our clinic. Levofloxacin in isolation failed to completely eliminate methicillin-susceptible *S. aureus*. Levofloxacin and rifampicin is the conventional antibiotic combination used to treat bone infections caused by *Staphylococcus aureus* and *P. aeruginosa*.

Determining the duration of cure time for an infection subsequent to bone infection treatment presents a challenging task. Urania Rappo [23] assessed the effectiveness of the infection treatment six weeks later. According to Daver NG [11], the infection is considered to be resolved if it does not reoccur within a period of six months. We assessed infection control six months following the procedure. The rate of abnormal ALT levels was considerably higher in the rifampicin group compared to the other groups, suggesting that postoperative combinations containing rifampicin may result in liver damage. Sahoko [24] further documented that rifampicin is capable of inducing acute renal injury. The results indicate that the three groups had an acceptable rate of complications overall. There was no significant difference in the recurrence rate between the IV group and the other two groups. Additionally, elevated ALT levels and proteinuria rates were observed in both the oral and rifampicin groups; the aberrant levels were likely the result of the additional oral

therapies. While the rifampicin group exhibited the highest incidence of proteinuria, there was no significant difference in the incidence of abnormal creatinine levels. This suggests that the additional rifampicin therapies could potentially induce early or modest renal damage.

Conclusion

Short-term antibiotic treatment regimens may achieve comparable rates of infection eradication following debridement of bone infections, while evading the potential renal and hepatic harm that is linked to extended antibiotic usage.

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