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Original Article

Factors that affect the duration of antimicrobial therapy for cellulitis

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ABSTRACT

Background: The recommended duration of antibiotic therapy for patients hospitalized with cellulitis is 5–14 days. However, factors that affect the duration of treatment have rarely been examined.
Methods: We conducted an observation study in a regional hospital in Japan to examine factors that affect the duration of antibiotic therapy for cellulitis. Our study included 102 patients with cellulitis of the lower extremities who were treated with intravenous cefazolin alone. Intravenous cefazolin was terminated when redness, swelling, and tenderness of the lower extremities disappeared, and subsequently the patients were discharged. The relationship between the duration (days) of treatment with intravenous cefazolin (DIVC) and clinical factors were analyzed.
Results: The median DIVC was 8 days (interquartile range, 7–10 days). On univariate analysis, DIVC correlated significantly with patient age ($P = 0.0071$) and with C-reactive protein levels before treatment ($P = 0.0053$). DIVC in patients with diabetes mellitus was significantly longer than that in patients without diabetes mellitus ($P = 0.0033$). DIVC in patients with blood stream infection was significantly longer than that in patients without blood stream infection ($P = 0.029$). On multivariate analysis, variables independently associated with longer DIVC included patient age ($P = 0.044$), C-reactive protein levels before treatment ($P = 0.017$), presence of diabetes mellitus ($P = 0.0021$), and presence of blood stream infection ($P = 0.028$).
Conclusions: Duration of treatment with intravenous antibiotics for cellulitis is associated with patient age, C-reactive protein levels, coexisting diabetes mellitus, and coexisting blood stream infection. These findings should be considered when treatment plans for cellulitis are devised.

1. Introduction

Cellulitis is an acute inflammatory condition of the dermis and subcutaneous tissue that is characterized by localized pain, erythema, swelling, and warmth. Since *Staphylococcus aureus* and streptococci are the most frequent causative pathogens, beta-lactam antibiotics with activity against penicillinase-producing *Staphylococcus aureus* are the usual drugs of choice [1].

Severe cellulitis requires initial treatment with intravenously administered antibiotics, which are delivered in the hospital in most countries, including Japan [2]. Then, patients should be switched to oral therapy when they are afebrile and when skin findings begin to resolve [1]. The recommended duration of antibiotic therapy for patients hospitalized with cellulitis is 5–14 days [1,3–5]. Recent studies of cellulitis have analyzed predisposing factors, causative pathogens, the usefulness of microbiological investigations, diagnostic imaging methods, and duration of hospitalization. However, factors that affect the duration of intravenous antibiotic therapy have rarely been examined [6]. Additionally, most studies that analyzed features associated with length of hospital stay or length of treatment included patients who were treated with heterogeneous antibiotics, and the heterogeneity may have affected the results of the analysis.

Cefazolin is a beta-lactam antibiotic against strains of gram-positive and gram-negative bacteria, including *Staphylococcus aureus* and streptococci [7]. The serum and tissue concentrations of cefazolin after intravenous administration were high enough to inhibit the strains of these bacteria [8]. A suggested regimen of cefazolin for the treatment of cellulitis is 1 g administered intravenously every 8 h [1,4,5,9]. We conducted an observation study in

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a single institution that clinically evaluated patients who were hospitalized for cellulitis of the lower extremities. All patients were treated with intravenous cefazolin. We examined factors that affected the duration of treatment with intravenous cefazolin.

2. Patients and methods

2.1. Patients

One hundred fifty-five patients with cellulitis were admitted to our hospital between November 2008 and May 2014. Of these patients, 137 developed cellulitis in the lower extremities; 15 developed cellulitis in the upper extremities; and three developed cellulitis in the trunk. Of the 137 patients with cellulitis of the lower extremities, 102 patients who were treated with intravenous cefazolin alone during their hospital stay were enrolled in this study. Therefore, 35 patients with cellulitis of the lower extremities were excluded. Exclusion criteria were as follows: patients treated with other antimicrobial agents due to renal failure; allergy to cefazolin; evidence of deep tissue infection, including necrotizing fasciitis and osteomyelitis; and isolation of cefazolin-resistant bacteria from erosive skin lesions. Patients who were initially treated with another antimicrobial agent intravenously by doctors from other departments were also excluded. Patients treated for a few days with oral antibiotics by a local physician before admission were included in this study. This study was approved by the ethics review board of Kanazawa Medical Center. Informed consent was obtained from each patient included in the study before starting treatment with intravenous cefazolin.

2.2. Diagnosis and treatment of cellulitis

A case of cellulitis was determined using the definition from the Infectious Diseases Society of America and the U.S. Food and Drug Administration for clinical trials [10]: “Cellulitis is a general descriptive term suggesting infection and indicating the warmth, erythema, and induration of the skin and/or subcutaneous tissue, with or without pain [11].” Erysipelas was distinguished clinically from cellulitis by the following two features: the lesions are raised above the level of the surrounding skin, and there is a clear line of demarcation between involved and uninvolved skin [12].

To confirm the diagnosis of cellulitis and to order an initial clinical laboratory test, one of the co-investigators (M.I. or C.N.) assessed the patients within 24 h of their initial visit to our hospital. Wound cultures were performed only when purulent material or serous discharge was obtained from a superficial site of infection. The co-investigators assessed the severity of cellulitis and advised patients with severe cellulitis who presented with high fever, marked redness and swelling, general malaise, strong pain, or disturbance in gait to be hospitalized for treatment. We instructed the nurses to perform a blood culture when the patients had high fever (>38 °C) during hospitalization. Informed consent was obtained, and 1 g of cefazolin was administered intravenously every 8 h. Adjustments for renal impairment were based on an estimate of creatinine clearance that reflects the glomerular filtration rate [4]. Intravenous administration of cefazolin was terminated when redness, swelling, and tenderness of the lower extremities disappeared. On weekends or holidays, either of the co-investigators (M.I. or C.N.) examined the patients and decided whether to terminate intravenous cefazolin therapy. We did not take C-reactive protein levels into consideration when we decided whether cefazolin should be terminated. Subsequently, the patients were discharged, and 78 patients were treated with oral antibiotics taken for 1 week.

2.3. Statistical analysis

The primary endpoint of this study was the duration (days) of treatment with intravenous cefazolin (DIVC). To check whether treatment with intravenous cefazolin terminated frequently or less frequently on a specific day(s) of the week, the chi-square goodness of fit test was used. To assess the factors that affect the duration of intravenous antibiotic therapy for cellulitis, we analyzed the relationship between DIVC and clinical data. Differences between clinical groups were calculated with the Mann–Whitney *U* test or the Kruskal–Wallis rank sum test. DIVC was expressed as a median with interquartile range (IQR). Since DIVC fit a log normal distribution, we also used the Student *t*-test and one-way analysis of variance test to compare the geometric means of DIVC in each subgroup, to check the results of non-parametric analysis. Because several of the selected variables did not fit a normal distribution or a log-normal distribution, correlation between DIVC and clinical variables were calculated with Spearman's rank correlation coefficient. In all tests, *P*-values less than 0.05 were considered statistically significant.

Multivariate analysis was performed after a logarithmic transformation of DIVC. For the multivariate analysis, we included all continuous variables and discrete variables at first and used the backward stepwise selection of variables. Potential confounding factors on admission that we considered in the analysis were sex, age, body mass index, site of cellulitis, pretreatment with oral antibiotics, C-reactive protein levels, white blood cell count, blood hemoglobin levels, lactate dehydrogenase levels, creatine phosphokinase levels, total protein levels, dose of cefazolin per weight, presence of diabetes mellitus, presence of heart failure, presence of decline in renal function (estimated creatinine clearance <50 mL/min), presence of venous stasis, presence of cutaneous ulcer, presence of dermatophytosis, and presence of blood stream infection.

All statistical analyses were performed with EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 3.1.1) [13]. More precisely, EZR is a modified version of R commander (version 2.1–2), designed to add statistical functions that are frequently used in biostatistics.

3. Results

3.1. Patient population and treatment outcome

During the study period, 137 patients with cellulitis of the lower extremities were admitted to our hospital. Cefazolin-resistant bacteria were isolated from erosive skin lesions of eight patients, and cefazolin was changed to another antimicrobial agent. One patient developed liver dysfunction after intravenous administration of cefazolin, and the treatment was discontinued. Furthermore, 26 patients were initially treated with an intravenous antimicrobial agent other than cefazolin. Thus, 102 patients with cellulitis of the lower extremities were treated with intravenous cefazolin alone and were included in our study.

Of the 102 patients, 51 (50%) were men. The median age was 73 years (range, 20–97 years) (Table 1). Locations of cellulitis were as follows: foot (n = 25), leg (n = 72), and both thigh and leg (n = 5). Dermatophytosis, cutaneous ulcer, venous stasis, diabetes mellitus, congestive heart failure, and decline in renal function are common comorbidities. Twenty-eight patients were treated with oral antibiotics before admission, and the antibiotics were as follows: cefcapene pivoxil (n = 10), levofloxacin (n = 10), cefdinir (n = 2), cefotiam hexetil (n = 2), cefpodoxime proxetil (n = 1), clarithromycin (n = 1), minocycline (n = 1), and tosufloxacin (n = 1). The dosing periods were as follows: 2 days (n = 12), 1 day (n = 7),

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