Effects of Prophylactic Antibiotic Administration and Antibiotic Timing on Culture Results and Clinical Outcomes of Pediatric Musculoskeletal Infection: A Protocol for A Randomized, Controlled, Clinical Trial

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Abstract

Background

Musculoskeletal infection (MSI) is a common cause of morbidity among the pediatric population. Some clinicians recommend withholding prophylactic antibiotics until culture collection with an aim to improve the culture sensitivity. However, a recent retrospective study reported that prophylactic antibiotic administration did not affect culture sensitivities in either disseminated or local MSI in pediatric population, which is surprising. Therefore, the aim of this study is to investigate the effects of prophylactic antibiotic administration and the timing of antibiotic administration on culture sensitivity and clinical outcomes of pediatric MSI.

Methods

A randomized, controlled, clinical trial will be carried out. Individuals aged 0 to 18 years with a diagnosis of MSI will be screened and evaluated at the Shenzhen Children's Hospital. The participants will be randomly allocated into four groups, and they will receive the antibiotic treatment at different time points, that is, 1 week, 3 days, 1 day prior to culture collection and 1 day after culture collection, respectively. The primary outcome will be culture sensitivity. In addition, the disease-related markers including white blood cell count (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate, vital signs as well as the length of hospital stay will be measured or recorded accordingly. Using chi-squared tests, the rates of positive cultures will be compared between different groups. Statistical comparisons between the different patient groups regarding the confounding and outcome variables will be conducted using independent t-tests, Mann-Whitney U tests, chi-squared tests and Fisher's exact tests as appropriate with the significance level set to 5% ($P < 0.05$).

Discussion

The results of this study would provide some evidence for the clinical management of pediatric MSIs with regards to the application of prophylactic antibiotics.

Trial registration

: Chinese Clinical Trial Registry, ChiCTR2100041631. Registered at 1 January 2021, http://www.chictr.org.cn/hvshowproject.aspx?id=69850.

Introduction

Musculoskeletal infection (MSI) in pediatric population is an ongoing condition due to continuous pathogenic changes. The incidence of pediatric MSIs is approximately 2–13 every 100,000 children per

year in developed countries but higher in other districts [1–4]. The MSIs consist of a wide spectrum of infections involving different musculoskeletal regions, including joint, bone, muscle and deep soft tissue. Historically, the clinical severity and presentation vary by the causative bacterium, and there has seen a significant change in osteoarticular infections pathogenesis due to emerging pathogens in the last decades [5, 6]. *Staphylococcus aureus methicillin susceptible* (MSSA) has been the most frequent cause of bone and joint infections, and *Kingella kingae* is the most frequent cause of osteoarticular infections in pediatric patients under 4 years. The emerging pathogens have added to the complexity of pediatric MSIs. The management of MSIs requires prompt diagnosis and treatment due to the risk of local tissue damage and metastatic bacterial spread. Culture is the main diagnostic method to identify the causative organism which could provide hints for the following targeted antibiotic therapy.

When caring for pediatric MSI patients, the question concerning the timing of prophylactic antibiotics remain controversial at present. Traditionally, some clinicians recommend that prophylactic antibiotics should be withheld until culture collection with the aim to improve the culturing sensitivity of the causative organisms and guide the application of antibiotics. However, in adults, conflicting studies on the effects of antibiotics on tissue culture results have been found [7–10]. Meanwhile, in other infectious diseases like sepsis [11–13], community-acquired pneumonia [14] and febrile neutropenia [15, 16], earlier antibiotic administration has shown some benefits. These conflicting findings have made it confusing when deciding whether to use prophylactic antibiotics prior to antibiotics in clinical practice. Nevertheless, a recent retrospective study surprisingly found that yields of tissue culture were not affected by antibiotic administration in either disseminated or local pediatric MSIs, and earlier antibiotic administration was correlated with shorter length of stay in children with local MSI [17]. In addition, another retrospective study reported that surgical culture yield in pediatric patients with acute, hematogenous, osteoarticular infection was not decreased by antibiotic administration 1 hour before surgery [18]. Besides, in a large retrospective study which included 710 pediatric MSI patients, no significant difference was found in the rate of blood-culture positivity between children who received antibiotics culture and those who did not [19]. These results suggested that antibiotic administration delay may not be necessarily needed for improving tissue culture results, which is quite a surprising suggestion. Therefore, a prospective trial is needed to further evaluate the effect of antibiotic timing in pediatric MSI tissue culture results.

A randomized, controlled, clinical trial will be carried out to (1) investigate whether the administration of routine prophylactic antibiotics administration would affect the culture sensitivity during MSI treatment; (2) evaluate the effects of the antibiotic timing on the yield of cultures and clinical outcomes. This study is aimed to provide some evidence for the clinical management of pediatric MSIs with regards to the application timing of antibiotics.

Methods

Study design and ethical issues

This protocol is a randomized controlled trial involving qualitative research, specimen (bone biopsy, fluid aspiration, etc.) collection and blood tests (Fig. 1). This trial has been developed according to the Standard Protocol Items: Recommendations for Intervention Trials 2013 statement [20]. The trial has received approval from the Human Research Ethics Committee of Shenzhen Children's Hospital. All the participants will sign the informed written consent before enrolled in the research.

Participants

Sample size

The software G*Power was used to generate a power analysis. Combining the results of comparable studies [21, 22] and theoretical considerations, the effect size was set as 0.8, the priori test power 1- β was 0.8, and the allocation ratio was 1. The software generates a minimum sample size of 26 patients for each group, which is enough to investigate this effect. The assumed dropout rate is approximately 20%. Therefore, the targeted sample size for each group should be 35, and a total of 140 patients will meet the criteria.

Inclusion criteria:

(1) Children and adolescents with a diagnosis of MSI;

(2) Aged 0–18 years;

(3) In agreement to participate in the clinical study.

Exclusion criteria:

Patients who have recently (within 4 weeks) received any antibiotic treatment no matter related or unrelated to the MSIs.

Interventions

The enrolled patients will be stratified into disseminated or local infection groups [23]. The patients will be randomly (using computer-generated random numbers generated by our statistician) divided into 4 groups, and will receive the antibiotic according to their allotment, that is, 1 week, 3 days, 1 day prior to culture collection and 1 day after, respectively. The participants will be blinded after assignment to interventions, and may be unblinded if deemed medically necessary by their provider and the study principal investigator.

Clinical outcome measures

Demographic data collection

The routine demographic data, including sex, age, classification of MSI, history of trauma, non-weight-bearing at presentation, and if previously seen by medical provider will be collected and recorded.

Culture

The bacterial culture will be carried out in the Medical Center Clinical Laboratory of Shenzhen Children's Hospital. Source specimens will be collected by experienced clinicians according to the classification of MSIs, i.e. fluid aspiration for septic arthritis, subperiosteal abscess when applicable, and pyomyositis, bone biopsy for osteomyelitis.

Blood test

Markers that indicate severity of disease at presentation including blood cell count (WBC), C-reactive protein (CRP), white erythrocyte sedimentation rate will be tested accordingly.

Length of hospital stay

Length of hospital stay of each participant will be recorded.

Patient and public involvement

Patients and/or the public were not directly involved in the design, or conduct, or reporting, or dissemination plans of this research.

Data and statistical analysis

The data will be tabulated (double data entry) and processed using GraphPad PRISM version 7.0 and the statistical analysis will be carried out using STATA Statistical Software (College Station, TX). The statistical comparison regarding the rates of positive cultures between the different groups will be conducted by Fisher's exact tests or chi-squares tests. The confounding and outcome variables will be compared between the different groups using chi-squared tests, Fisher's exact tests or independent *t*-tests will be used as appropriate with the significance level set to 5% ($P < 0.05$).

Discussion

The main objective of the clinical trial is to investigate whether the administration of prophylactic antibiotics will decrease the rates of positive culture of pediatric MSI treatment and to evaluate the effects of the antibiotic timing on the culture sensitivity and clinical outcomes. We hope that the results of this study would provide some evidence for the clinical management of pediatric MSIs with regards to the application of antibiotics. If the administration of prophylactic antibiotics does not decrease the culture sensitivity of pediatric MSI patients, then it is suggested that appropriate systemic antibiotics should be given to pediatric patients presenting with suspected MSIs promptly after clinical triage.

Abbreviations

CRP
C-reactive protein; MSI:musculoskeletal infection; MSSA:Staphylococcus aureus methicillin susceptible; WBC:white blood cell count.

Declarations

Declaration of conflict of interest

The authors have no conflicts of interest to disclose.

Funding

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YJX, CD, and CY conceived of the idea, YJX, YBZ and DCW developed the intervention, YJX, LFX, BE and CY developed the design of the trial and wrote the article. YJX and JMH did the literature research. All authors have read and approved the final manuscript.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Ethics approval and consent to participate

The study design, procedures and informed consent procedure were approved by the Human Research Ethics Committee of Shenzhen Children's Hospital (No.SZCH2020123001). The approval was obtained on December 30, 2020. Consent to participate will be obtained from the participants.

Consent for publication

Not acquired

Trial status

Approval by the Human Research Ethics Committee of Shenzhen Children's Hospital was received 30th of December 2020 (No.SZCH2020123001), and patient recruitment has not started yet.

Assessment Schedule

This article has been written according to the guidelines for content of clinical trial protocols (SPIRIT) with a checklist (Additional file 1).

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Figures

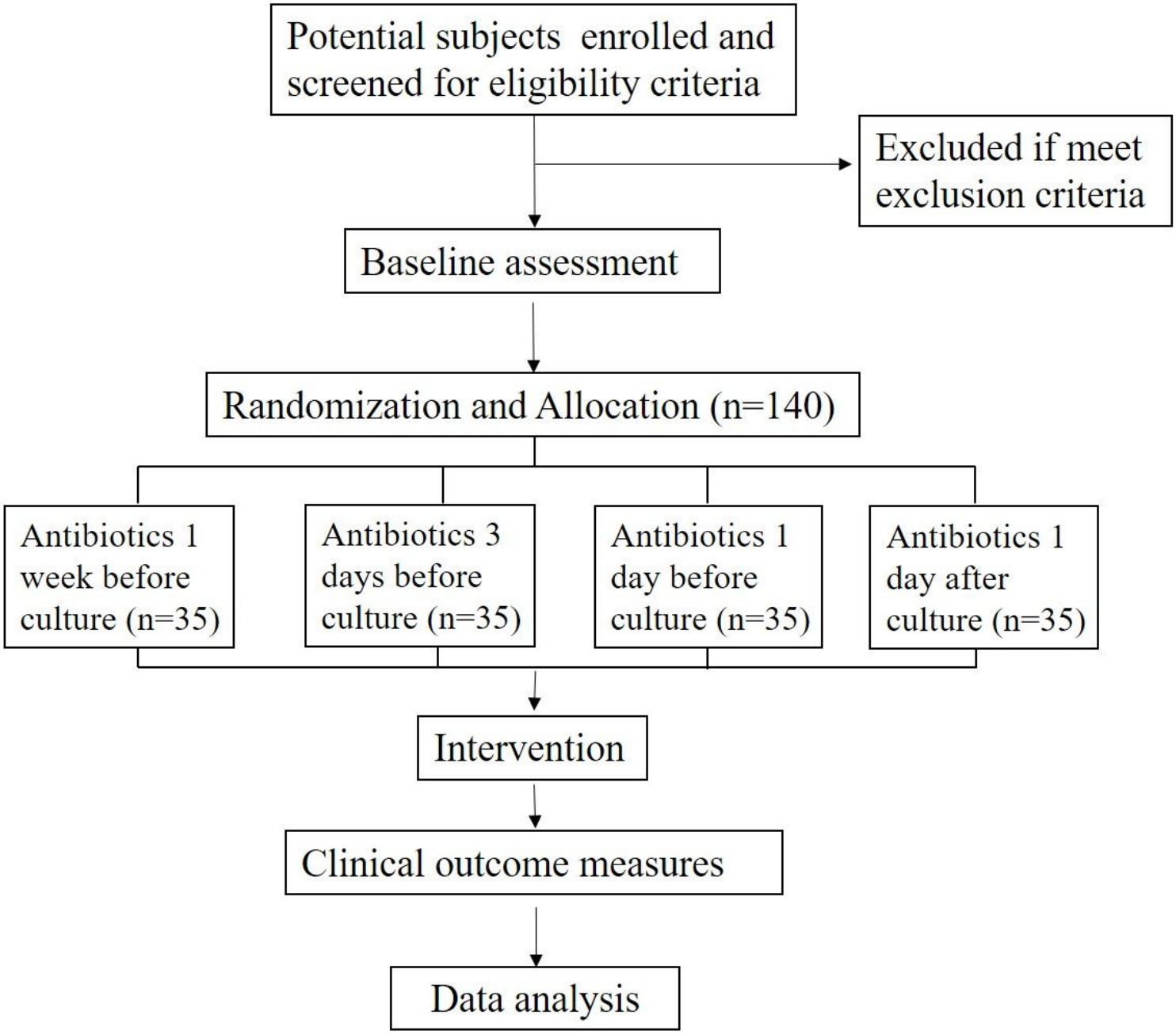

Figure 1

Schematic diagram of the study flow

Supplementary Files

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- SPIRITchecklist.docx