Effects of prophylactic antibiotic administration and antibiotic timing on culture results and clinical outcomes of paediatric musculoskeletal infection: a protocol for a randomised controlled clinical trial

Yongjie Xia, Chao Deng, Yibiao Zhou, Dechao Wu, Zhiyong Liu, Liangfu Xie, Bing E, Jingming Han, Chao You

ABSTRACT

Introduction Musculoskeletal infection (MSI) is a common cause of morbidity among the paediatric 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 paediatric population, which is surprising. The aim of the present study is to investigate the effects of prophylactic antibiotic administration and the timing of antibiotic administration on culture sensitivity and clinical outcomes of paediatric MSI.

Methods and analysis A randomised controlled clinical trial will be carried out. Individuals aged 0–18 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 tissue culture collection and 1 day after tissue culture collection, respectively. The primary outcome will be culture sensitivity. In addition, the disease-related markers including white blood cell count, C reactive protein, erythrocyte sedimentation rate, vital signs as well as the length of hospital stay will be measured or recorded accordingly. Using χ² 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, χ² tests and Fisher’s exact tests as appropriate with the significance level set to 5% (p<0.05).

Ethics and dissemination This study has received ethical approval. The findings will be disseminated both in scientific conferences and peer-reviewed journal.

Trial registration number ChiCTR2100041631.

INTRODUCTION

Musculoskeletal infection (MSI) in paediatric population is an ongoing condition due to continuous pathogenic changes. The incidence of paediatric MSIs is approximately 2–13 every 100 000 children per year in high-income countries but higher in other districts. The MSIs consist of a wide spectrum of infections involving different musculoskeletal districts, including joint, bone, muscle and deep soft tissue. Historically, the clinical severity and presentation vary by the causative bacterium, and there has been a significant change in osteoarticular infections pathogenesis due to emerging pathogens in the last decades. Methicillin-susceptible Staphylococcus aureus has been the most frequent cause of bone and joint infections, and Kingella kingae is the most frequent cause of osteoarticular infections in paediatric patients under 4 years. The emerging pathogens have added to the complexity of paediatric 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 pathogens in the last decades.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a single-centre study, and the results may need further verification in multicentre studies.
⇒ The results of this study would provide some evidence for the clinical management of paediatric MSIs with regard to the application of antibiotics.
⇒ This trial is the first prospective trial to investigate the effects of prophylactic antibiotic administration and the timing of antibiotic administration on culture sensitivity and clinical outcomes of paediatric musculoskeletal infections (MSIs).
organism, which could provide hints for the following targeted antibiotic therapy.

When caring for paediatric patients with MSI, 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 guiding the application of antibiotics. However, in adults, conflicting studies on the effects of antibiotics on tissue culture results have been found. Meanwhile, in other infectious diseases like sepsis, community-acquired pneumonia and febrile neutropenia, 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 paediatric MSIs. In addition, another retrospective study reported that surgical culture yield in paediatric patients with acute, hematogenous, osteoarticular infection was not decreased by antibiotic administration 1 hour before surgery. These results suggested that antibiotic administration delay may not be necessarily needed for better tissue culture results, which is quite a surprising suggestion. Therefore, a prospective trial is needed to further evaluate the effect of antibiotic timing on paediatric MSI tissue culture results.

A randomised 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 paediatric MSIs with regard to the application timing of antibiotics.

METHODS AND ANALYSIS

Participants

Sample size

The software PASS V.15.0 was used to generate a power analysis. Combining the results of comparable studies and theoretical considerations, the effect size was set as 0.25, the a priori test power 1−β was 0.8 and the allocation ratio was 1. The software generates a minimum sample size of 126 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 158, and a total of 632 patients will meet the criteria (figure 1).

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 with signed informed consent (online supplemental file).

Exclusion criteria

1. Patients with evidence of current infections such as chronic recurrent multifocal osteomyelitis, poststreptococcal disease, necrotising fasciitis, cellulitis or other fungal or mycobacterial infections.
2. Patients who have recently (within 4 weeks) received any antibiotic treatment no matter related or unrelated to the MSIs.
3. Patients from whom the tissue culture is taken 7 days after initiation of antimicrobial therapy.

Figure 1 Flowchart of the study. The eligible participants are assessed and grouped randomly. Clinical outcomes are measured after interventions are given and the related data are analysed.
The interventions
The enrolled patients will be stratified into disseminated or local infection groups. The patients will be randomly (using computer-generated random numbers) divided into four 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.

For culture-negative cases, imaging techniques will be applied for differential diagnosis. For culture-negative but highly suspected cases, real-time PCR will be applied to exclude the pathogens that are difficult to detect in culture, such as K. kingae. However, it is also difficult to detect pathogens like S. aureus even using real-time PCR. Thus, the exclusion of MSI infection and the decision of early switch to oral therapy in culture-negative cases are prudently proceeded in our current approach.

For the culture-negative but with imaging or other evidence supporting MSI cases, the duration of hospitalisation is the same as infection-confirmed cases. For culture-negative and primary aetiology confirmed cases, the duration of hospitalisation is determined based on the primary diseases. For culture-negative and primary aetiology unconfirmed cases, the duration of hospitalisation is determined according to the general condition of the patient.

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, that is, 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 white blood cell count, C reactive protein, white erythrocyte sedimentation rate will be tested accordingly.

Length of hospital stay
Length of hospital stay of each participant will be recorded.

Follow-up
Clinical outcomes at 6 weeks and 6 months after completion of therapy are collected during the follow-up.

Data and statistical analysis
The data will be tabulated and processed using GraphPad PRISM V.7.0 and the statistical analysis will be carried out using STATA Statistical Software (College Station, Texas, USA). The statistical comparison regarding the rates of positive cultures between the different groups will be conducted by Fisher’s exact tests or $\chi^2$ tests. The confounding and outcome variables will be compared between the different groups using $\chi^2$ tests, Fisher’s exact tests or independent t-tests will be used as appropriate with the significance level set to 5% (p<0.05).

ETHICS AND DISSEMINATION
This protocol is a randomised controlled trial involving qualitative research, specimen (bone biopsy, fluid aspiration, etc) collection and blood tests. 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. The findings will be disseminated both in scientific conferences and peer-reviewed journal.

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 paediatric 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 paediatric MSIs with regard to the application of antibiotics. If the administration of prophylactic antibiotics does not decrease the culture sensitivity of paediatric MSI patients, then it is suggested that appropriate systemic antibiotics should be given to paediatric patients presenting with suspected MSIs promptly after clinical triage.

Twitter Yongjie Xia @Not available
Contributors CY was responsible for the conception of the study. YX and CD drafted the initial manuscript. YZ, DW and ZL contributed to data management. LX, BE and JH performed the analysis. All authors participated in the refinement of the protocol.
Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.
Competing interests None declared.
Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.
Patient consent for publication Not applicable.
Provenance and peer review Not commissioned; externally peer reviewed.
Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.
Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is

Xia Y, et al. BMJ Open 2022;12:e053568. doi:10.1136/bmjopen-2021-053568
REFERENCES

1. Gafur OA, Copley LAB, Hollmig ST, et al. The impact of the current epidemiology of pediatric musculoskeletal infection on evaluation and treatment guidelines. *J Pediatr Orthop* 2008;28:777–85.

2. Riise Øystein Rolandsen, Kirkhus E, Handeland KS, et al. Childhood osteomyelitis-incidente and differentiation from other acute onset musculoskeletal features in a population-based study. *BMC Pediatr* 2008;8:45.

3. Dartnell J, Ramachandran M, Katchburian M. Haematogenous acute and subacute paediatric osteomyelitis: a systematic review of the literature. *J Bone Joint Surg Br* 2012;94:584–95.

4. Rossaak M, Pitto RP. Osteomyelitis in Polynesian children. *Int Orthop* 2005;29:55–8.

5. Dodwell ER. Osteomyelitis and septic arthritis in children: current concepts. *Curr Opin Pediatr* 2013;25:58–63.

6. Arnold SR, Elias D, Buckingham SC, et al. Changing patterns of acute hematogenous osteomyelitis and septic arthritis: emergence of community-associated methicillin-resistant Staphylococcus aureus. *J Pediatr Orthop* 2006;26:703–8.

7. Ghanem E, Parvizi J, Klohisy J, et al. Perioperative antibiotics should not be withheld in proven cases of periprosthetic infection. *Clin Orthop Relat Res* 2007;461:44–7.

8. Choi H-R, Kwon Y-M, Freiberger AA, et al. Periprosthetic joint infection with negative culture results: clinical characteristics and treatment outcome. *J Arthroplasty* 2013;28:899–903.

9. Al-Mayahi M, Cian A, Lipsky BA, et al. Administration of antibiotic agents before intraoperative sampling in orthopedic infections alters culture results. *J Infect* 2015;71:158–25.

10. Shahi A, Deirmengian C, Higuera C, et al. Premature therapeutic antimicrobial treatments can compromise the diagnosis of late periprosthetic joint infection. *Clin Orthop Relat Res* 2015;473:2244–9.

11. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Cirt Care Med* 2014;42:1749–55.

12. Gaiieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med* 2010;38:1045–53.

13. Kianar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;34:1589–96.

14. Huang JQ, Hooper PM, Marrie TJ. Factors associated with length of stay in hospital for suspected community-acquired pneumonia. *Can Respir J* 2006;13:317–24.

15. Perron T, Emara M, Ahmed S. Time to antibiotics and outcomes in cancer patients with febrile neutropenia. *BMJ Health Serv Res* 2014;14:162.

16. Pfielder M, Hodgkiiss H, Zhang S, et al. Prompt administration of antibiotics is associated with improved outcomes in febrile neutropenia in children with cancer. *Pediatr Blood Cancer* 2013;60:1299–306.

17. Benvenuti MA, An TJ, Migneri ME, et al. Effects of antibiotic timing on culture results and clinical outcomes in pediatric musculoskeletal infection. *J Pediatr Orthop* 2019;39:158–62.

18. van der Merwe M, Rooks K, Crawford H, et al. The effect of antibiotic timing on culture yield in paediatric osteoarticular infection. *J Child Orthop* 2019;13:114–9.

19. Burnett RSJ, Aggarwal A, Givens SA, et al. Prophylactic antibiotics do not affect cultures in the treatment of an infected TKA: a prospective trial. *Clin Orthop Relat Res* 2010;468:127–34.

20. Diamini LD, Sekikubo M, Tumukunde J, et al. Antibiotic prophylaxis for caesarean section at a Ugandan Hospital: a randomised clinical trial evaluating the effect of administration time on the incidence of postoperative infections. *BMC Pregnancy Childbirth* 2015;15:91.

21. Garin EH, Olavarria F, Garcia Nieto V, Nieto G V, et al. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. *Pediatrics* 2006;117:626–32.

22. Migneri ME, Benvenuti MA, An TJ, et al. A novel classification system based on dissemination of musculoskeletal infection is predictive of hospital outcomes. *J Pediatr Orthop* 2018;38:279–86.

23. Ilharreborde B, Bidet P, Lorrot M, et al. New real-time PCR-based method for Kingella kingae DNA detection: application to samples collected from 89 children with acute arthritis. *J Clin Microbiol* 2009;47:1837–41.

24. Haldar M, Butler M, Quinn CD, et al. Evaluation of a real-time PCR assay for simultaneous detection of Kingella kingae and Staphylococcus aureus from synovial fluid in suspected septic arthritis. *Ann Lab Med* 2014;34:313–6.