INPLASY PROTOCOL

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Conflicts of interest: **All authors involved in this work have no conflicts of interest.**

Adjunctive Rifampin Therapy For Diabetic Foot Osteomyelitis: A Systematic Review and Meta-Analysis

Zhang, YL[1]; Wang, SJ[2]; Liu, M[3]; Yao, SS[4]; Fang, S[5]; Cheng, HP[6]; Chen Q[7].

Review question / Objective: **Amputation is a serious and unfortunate consequence of lower limb osteomyelitis in patients with diabetes.Among patients diagnosed with diabetes, the lifetime incidence of foot ulcers is 15%.Infection is a common complication of foot ulcers, and 20% to 60% of infections result in diabetic foot osteomyelitis (DFO). When a foot infection in a patient with diabetes extends to bone (diabetic foot osteomyelitis [DFO]), a 4-fold increased risk of amputation is present. Current treatment guidelines do not endorse any specific antibiotic agent for DFO, but small clinical trials suggest the addition of rifampin to antimicrobial regimens results in improved cure rates for osteomyelitis.**
Condition being studied: **Amputation is a serious and unfortunate consequence of lower limb osteomyelitis in patients with diabetes. Among patients diagnosed with diabetes, the lifetime incidence of foot ulcers is 15%.Infection is a common complication of foot ulcers, and 20% to 60% of infections result in diabetic foot osteomyelitis (DFO). Current treatment guidelines do not endorse any specific antibiotic agent for DFO, but small clinical trials suggest the addition of rifampin to antimicrobial regimens results in improved cure rates for osteomyelitis. It is hoped that adjunctive rifampin therapy may be a useful antimicrobial strategy in the treatment of DFO.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 April 2020 and was last updated on 11 April 2020 (registration number INPLASY202040058).

INTRODUCTION

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complication of foot ulcers, and 20% to 60% of infections result in diabetic foot osteomyelitis (DFO). When a foot infection in a patient with diabetes extends to bone (diabetic foot osteomyelitis [DFO]), a 4-fold increased risk of amputation is present. Current treatment guidelines do not endorse any specific antibiotic agent for DFO, but small clinical trials suggest the addition of rifampin to antimicrobial regimens results in improved cure rates for osteomyelitis.

Condition being studied: Amputation is a serious and unfortunate consequence of lower limb osteomyelitis in patients with diabetes. Among patients diagnosed with diabetes, the lifetime incidence of foot ulcers is 15%.Infection is a common complication of foot ulcers, and 20% to 60% of infections result in diabetic foot osteomyelitis (DFO). Current treatment guidelines do not endorse any specific antibiotic agent for DFO, but small clinical trials suggest the addition of rifampin to antimicrobial regimens results in improved cure rates for osteomyelitis. It is hoped that adjunctive rifampin therapy may be a useful antimicrobial strategy in the treatment of DFO.

METHODS

Search strategy: The English databases we searched are PubMed, Embase, Cochrane Library Central Register of Controlled Trials and Web of Science; Chinese databases include China National Knowledge Infrastructure (CNKI) database, Wanfang Data Knowledge Service Platform, the VIP information resource integration service platform (cqvip), China Biology Medicine Disc (Sino Med) with a language limitation of English and Chinese. In addition, we searched Google Scholar, Baidu Scholar, and unpublished research and other related literature, most importantly, we manually searched the Chinese Clinical Trial Registry (ChiCTR) and ClinicalTrial.gov related research in the Chengdu University of Traditional Chinese Medicine Library. We use keyword and free word combination as the basic search strategy. The search criteria are as follows: "Diabetic foot", "Foot, Diabetic", "Diabetic Feet", "Feet, Diabetic", "Foot Ulcer, Diabetic", "osteomyelitis", "Osteomyelitides", "rifampin", "Benemycin","Rifampicin", "Rimactan", "Tubocin", "Rifadin", "Rimactane".

Participant or population: Regardless of age, gender, ethnicity, and other factors, patients who met the DFO diagnostic criteria of the International Diabetes Working Group were included. Exclude patients who are using the drug with contraindications to rifampicin and patients who are allergic or intolerant to rifampicin.

Intervention: Both groups of patients received the routine diabetes treatment recommended by the ADA guidelines, including diet, exercise, hypoglycemic, lipid-lowering and other basic treatments of diabetic foot. The test group was given rifampicin, and the control group was given other antibiotics, placebo or no drugs. In addition, neither group of patients can take drugs that interfere with the outcome indicators, and the treatment time is ≥6 weeks.

Comparator: The test group was given rifampicin, and the control group was given other antibiotics, placebo or no drugs.

Study designs to be included: This study only selected clinical randomized controlled studies of rifampicin for the adjuvant therapy of DFO.

Eligibility criteria: Regardless of age, gender, ethnicity, and other factors, patients who met the DFO diagnostic criteria of the International Diabetes Working Group were included.

Information sources: The English databases we searched are PubMed, Embase, Cochrane Library Central Register of Controlled Trials and Web of Science; Chinese databases include China National Knowledge Infrastructure (CNKI) database, Wanfang Data Knowledge Service Platform, the VIP information resource integration service platform (cqvip), China Biology Medicine Disc (Sino Med) with a

language limitation of English and Chinese. In addition, we searched Google Scholar, Baidu Scholar, and unpublished research and other related literature, most importantly, we manually searched the Chinese Clinical Trial Registry (ChiCTR) and ClinicalTrials.gov related research in the Chengdu University of Traditional Chinese Medicine Library.

Main outcome(s): The primary outcomes of this study include evaluating the difference between the efficacy of adjuvant treatment for DFO with and without rifampin, That is to evaluate the effect of rifampicin in the treatment of DFO on amputation rate and mortality in patients with diabetic foot.

Additional outcome(s): The secondary outcomes mainly included the survival rate of unamputeed patients, changes in glycated hemoglobin, serum creatinine, ulcer area, and assessment of patient quality of life by SF-36.

Quality assessment / Risk of bias analysis: Each randomized controlled trial included requires an assessment of its risk of bias, and the two reviewers will use the Cochrane Collaboration tool to assess the risk of bias in the included article. This is a more reliable tool for assessing the risk of research bias. There are 7 items to assess the risk of bias in the trial: random sequence generation (selection bias), allocation of hidden (selection bias), participant and human blindness (performance bias), outcome evaluation blindness (detection bias), incomplete outcome data (Loss bias), selective reporting (reporting bias), and other biases. Each project is classified as "low risk", "high risk" or "unclear risk". The risk of bias will be assessed independently by two reviewers and any differences will be resolved through discussion by all reviewers.

Strategy of data synthesis: We will perform a meta-analysis of all statistics using Revman 5.3 software provided by Cochrane Collaboration, use 95% confidence intervals (CI) and risk ratio (RR) to calculate categorical variables, and use 95% CI and mean difference (MDs) Calculate continuous variables. If there is no heterogeneity in the trial, study design of participants, controls, interventions, and outcome measures ($I2 < 50\%$, $P > 0.1$), the data are synthesized using a fixed effects model. Otherwise ($I2 \geq 50\%$, $P < 0.1$), a random effects model will be used for analysis. Finally, subgroup analysis was performed based on different causes of heterogeneity, and if meta-analysis was not available, it was replaced with general descriptive analysis.

Subgroup analysis: If the results of the study are heterogeneous, we will conduct a subgroup analysis for different reasons. Heterogeneity is manifested in the following several aspects, such as race, age, gender, different intervention forms, pharmaceutical dosage, treatment course.

Sensibility analysis: Exclude each study included in the analysis one by one, re-analyze and summarize the data, and compare the differences between the retrieved results and the original results. Therefore, we will be able to discover the impact of individual studies on overall results and whether the results are reliable.

Keywords: Diabetic Foot, Osteomyelitis, rifampin, protocol, systematic review and meta-analysis.

Dissemination plans: This study systematically evaluated the existing research evidence of rifampicin adjuvant therapy DFO, which will certainly provide evidence-based medicine support for clinical workers. Our findings will be published in a peer-reviewed journal.

Contributions of each author:
Author 1 - Yanli Zhang proposed concept, retrieved literatures, managed data, analyzed data , and drafted manuscript.
Author 2 - Shengju Wang managed data, analyzed data , and drafted manuscript.
Author 3 - Min Liu contributed to the development of the selection criteria, and the risk of bias assessment strategy.

Author 4 - Shasha Yao read, provided feedback and approved the final manuscript.
Author 5 - Song Fang contributed to the research selection.
Author 6 - Haiping Cheng contributed to the assessment of the quality of grade.
Author 7 - Qiu Chen given fund support, manuscript revision.