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Review

Meta-analysis of ceftriaxone compared with penicillin for the treatment of syphilis

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ABSTRACT

Penicillin is the gold standard for treating syphilis. However, allergic reactions, poor drug tolerance and limited efficacy in patients remain a challenging problem. The objective of this meta-analysis was to compare the efficacy of ceftriaxone and penicillin based on data obtained from published randomised controlled trials (RCTs). The Cochrane Library, Medline, EBSCO, EMBASE and Ovid databases were searched for RCTs of ceftriaxone vs. penicillin for the treatment of syphilis. Estimated risk ratios (RRs) and 95% confidence intervals (CIs) were used to investigate the following outcome measures: 3-month response rate; 6-month response rate; 12-month response rate; relapse rate; serofast rate; and failure rate. Seven RCTs involving 281 participants (159 patients who received ceftriaxone and 122 patients who received penicillin) were included in the meta-analysis. There were no significant differences in 3-month response rate (RR = 1.12, 95% CI 0.89–1.42), 6-month response rate (RR = 1.02, 95% CI 0.75–1.38), 12-month response rate (RR = 1.04, 95% CI 0.82–1.32), relapse rate (RR = 0.91, 95% CI 0.45–1.84), serofast rate (RR = 0.69, 95% CI 0.22–2.12) or failure rate (RR = 0.66, 95% CI 0.03–15.76) in patients treated with ceftriaxone compared with those treated with penicillin. In conclusion, there is no evidence in the literature that ceftriaxone is less efficient than penicillin.

1. Introduction

Syphilis is a sexually transmitted disease caused by infection with the spirochete *Treponema pallidum* [1]. Clinical manifestations of syphilis include meningeal and central nervous system (CNS) symptoms, which can occur early in the course of untreated disease [2]. Syphilis infections arise in various subpopulations owing to changing sexual and social norms, outbreaks in individuals infected with human immunodeficiency virus (HIV), substance abuse, global travel and migration, and underinvestment in public health services. Globally, there are great variations in the incidence of syphilis, and the disease is most prevalent in developing countries as well as among poor and marginalised people [3].

Penicillin has been recommended as the mainstay of treatment for all types of syphilis since it was first used for this indication in 1943 [4]. However, penicillin cannot be used in up to 10% of individuals owing to allergic reactions [5], and treatment failures can occur, particularly in individuals with HIV co-infection and in cases of neurosyphilis. There is an unmet need for novel treatment options in syphilis-infected individuals who are allergic or intolerant to penicillin.

Ceftriaxone, a third-generation cephalosporin antibiotic, is a promising alternative to penicillin for the treatment of syphilis. It is well tolerated, has good CNS penetration and effectiveness for neurosyphilis, including asymptomatic forms, and has a long half-life that enables once-daily dosing [6,7]. Randomised controlled trials (RCTs) have compared the efficacy of ceftriaxone and penicillin for the treatment of syphilis; however, the efficacy of ceftriaxone remains controversial.

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The objective of this meta-analysis was to compare the efficacy of ceftriaxone and penicillin for the treatment of syphilis based on data from published RCTs.

2. Materials and methods

2.1. Search strategy

The Cochrane Library, Medline, EBSCO, EMBASE and Ovid databases as well as clinical trial websites (1 January 1988 to 5 January 2014) were searched. Search terms were based on MeSH words or keywords using the following search terms: 'ceftriaxone' OR 'penicillin' OR 'syphilis' AND 'randomised controlled trials'. Additional information was retrieved through a hand search of the reference lists from relevant articles. No language restrictions were applied.

2.2. Inclusion and exclusion criteria

Inclusion criteria were RCTs that: (i) reported on treatments of early syphilis including primary, secondary and latent stages; (ii) compared penicillin vs. ceftriaxone; (iii) included patients with no history of allergy to ceftriaxone or penicillin; (iv) had no restriction on nationality and ethnicity of research subjects; and (v) reported sufficient data on outcomes of interest.

Exclusion criteria were: (i) non-randomised and non-clinical controlled trials; (ii) trials with missing data [e.g. total number of patients, 3-, 6- or 12-month response rates, and relapse, serofast (the nontreponemal antibody test results remain in a tight range 1 year after the recommended therapy) [8] and failure rates]; and (iii) duplicate reports, trials of poor methodological quality and trials with obvious bias.

2.3. Study selection

Two investigators (G.J. and Y.-P.C.) independently examined the titles and abstracts to select eligible studies. The full text of potentially relevant studies was retrieved. Two review authors (Z.L. and W.G.) independently examined the full-text records to determine which studies met the inclusion criteria. Disagreement regarding study selection was resolved by discussion and consensus with another investigator (X.-X.J.).

2.4. Data extraction

Two investigators (G.J. and Y.-P.C.) independently extracted information from eligible studies. Data included the name of the first author, year of publication, quality of the study, stage of syphilis, intervention, median patient age, number of patients in the study, dosage and duration of ceftriaxone or penicillin, and outcomes.

The outcomes of interest were treatment efficacy at 3-, 6- and 12 months of follow-up and included (i) response rates and (ii) relapse rates, serofast rates using nontreponemal antigen test changes in serum titres, and failure rates. Response was defined as a ≥4-fold decrease in Venereal Disease Research Laboratory Test/rapid plasma reagin (VDRL/RPR) titre with no increase during the observation period. Relapse was defined as a ≥4-fold decrease in VDRL/RPR titre followed by a return to the original level or higher. Serofast was defined as a persistent titre of VDRL/RPR after syphilis treatment, whereby no change in titre occurred during the follow-up period, and no signs of clinical progression. Failure was defined as a ≥4-fold rise in VDRL/RPR without an initial response, a persistent titre of ≥1:64, or clinical progression of the disease. Disagreement regarding data extraction was resolved by discussion and consensus with another investigator (X.-X.J.).

2.5. Quality assessment

Two investigators (G.J. and Y.-P.C.) used the '*Cochrane handbook for systematic reviews of interventions version 5.0.0*' to assess the methodological quality of the included RCTs, which assessed: (i) generation of the random allocation scheme (random sequence generation); (ii) allocation concealment; (iii) blinding of participants and personnel; (iv) blinding of outcome assessment; (v) incomplete outcome data; (vi) selective reporting; and (vii) other sources of bias.

2.6. Statistical methods

Statistical analyses were conducted using Review Manager v.5.0 software (Cochrane Collaboration, Oxford, UK). For dichotomous variables, outcomes were reported as relative risk ratio (RR) and 95% confidence interval (CI). A *P*-value of <0.05 was considered statistically significant.

Heterogeneity among studies was determined by χ^2-based *Q*-test and I^2 test [9,10]. A fixed-effects model was used for outcome data with evidence of low heterogeneity ($P > 0.1$; $I^2 \leq 50\%$). For outcome data with evidence of significant heterogeneity ($P < 0.1$; $I^2 > 50\%$), trials were analysed to identify the contributing factors. If heterogeneity was not clinically significant, a random-effects model was applied. Sensitivity analysis was conducted to confirm whether the results were robust and reliable [11].

3. Results

Two investigators independently selected literature on the basis of the inclusion and exclusion criteria [12,13]. The literature selection process is presented in the PRISMA flow chart (Fig. 1) according to the PRISMA guidelines. The searches identified 969 potential articles, and 80 studies were identified as potentially eligible for inclusion. After analysing the full-text articles, 73 studies were excluded and seven RCTs were found eligible for inclusion according to the criteria for this review [14–20].

3.1. Included studies

In total, 281 patients were enrolled in the included RCTs. Patients were aged 18–61 years and were experiencing primary, secondary or latent stage syphilis. Of the 281 patients, 159 received ceftriaxone and 122 received penicillin. Drugs were administered intramuscularly or intravenously. The characteristics of the seven included RCTs are shown in Table 1.

Of the 73 excluded studies, 12 studies only reported efficacy results for penicillin or ceftriaxone, 9 studies compared penicillin with a drug other than ceftriaxone, and 52 studies were not RCTs.

3.2. Methodological quality of included studies

Of the seven RCTs that were included in this study, all seven studies mentioned the randomisation method and that allocation concealment was conducted, and three of the studies had incomplete outcome data (Fig. 2).

3.3. Three-month response rate

Data reporting on 3-month response rate to treatment were described in three RCTs. The meta-analysis demonstrated no significant difference in the 3-month response rate in patients treated with ceftriaxone compared with those treated with penicillin