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Review

Continuous versus intermittent infusion of vancomycin in adult patients: A systematic review and meta-analysis

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ABSTRACT

Continuous infusion of vancomycin (CIV) and intermittent infusion of vancomycin (IIV) are two major administration strategies in clinical settings. However, previous articles comparing the efficacy and safety of CIV versus IIV showed inconsistent results. Therefore, a meta-analysis was conducted to compare the efficacy and safety of CIV and IIV. PubMed, the Cochrane Library and Web of Science up to June 2015 were searched using the keywords 'vancomycin', 'intravenous', 'parenteral', 'continuous', 'intermittent', 'discontinuous', 'infusion', 'administration' and 'dosing'. Eleven studies were included in the meta-analysis. Neither heterogeneity nor publication bias were observed. Patients treated with CIV had a significantly lower incidence of nephrotoxicity compared with patients receiving IIV [risk ratio (RR) = 0.61, 95% confidence interval (CI) 0.47–0.80; $P < 0.001$]. No significant difference in treatment failure between the two groups was detected. Mortality between patients receiving CIV and patients receiving IIV was similar (RR = 1.15, 95% CI 0.85–1.54; $P = 0.365$). This meta-analysis showed that CIV had superior safety compared with IIV, whilst the clinical efficacy was not significantly different. A further multicentre, randomised controlled trial is required to confirm these results.

1. Introduction

Vancomycin is commonly prescribed as empirical coverage for drug-resistant Gram-positive organisms, especially for meticillin-resistant *Staphylococcus aureus* (MRSA). In recent years, the occurrence of clinical failure in patients with severe MRSA infections has increased dramatically [1–3]. However, due to limitations in the introduction of advanced antibiotics into clinical practice and the development of novel antibiotics [4], alternative administration strategies of vancomycin have been investigated to improve clinical efficacy.

Consensus guidelines recommend that vancomycin be administered by intermittent infusion [5,6]. However, recent research suggests that continuous infusion of vancomycin (CIV) may have some advantages over intermittent infusion of vancomycin (IIV) [7,8].

Several parameters have been identified to measure the efficacy of vancomycin, such as the duration that the drug serum concentration exceeds the minimum inhibitory concentration (MIC) of the target organism ($T_{>MIC}$) [9,10] and the serum drug area under the concentration–time curve (AUC) to MIC ratio (AUC/MIC) [5,8,11]. Previous studies showed that CIV had the potential to increase the $T_{>MIC}$ [12]. The occurrence of vancomycin-associated toxicity related to a high-dose regimen and high trough serum level has been reported [13]. However, published articles and reviews comparing the efficacy and safety of CIV versus IIV showed inconsistent results [14–38].

A meta-analysis published by Cataldo et al. suggested that CIV was associated with a significantly lower risk of nephrotoxicity compared with IIV, whereas it did not show an obvious superior impact on mortality rate or on pharmacodynamic activity in terms of AUC/MIC ratio [34]. However, several clinical studies have been carried out to compare the efficacy and safety of CIV with IIV since then [25–28,30]. Therefore, we believe that different or new results might be identified. Thus, the newly published studies were enrolled in the present study and a systematic review and meta-analysis was conducted. The aim was to illustrate the clinical efficacy and safety of CIV compared with IIV in adult patients with infections.

2. Methods

The method of the study was previously specified and documented in a protocol on the website of PROSPERO (http://www.crd.york.ac.uk/PROSPERO/; registration no. CRD42015015396).

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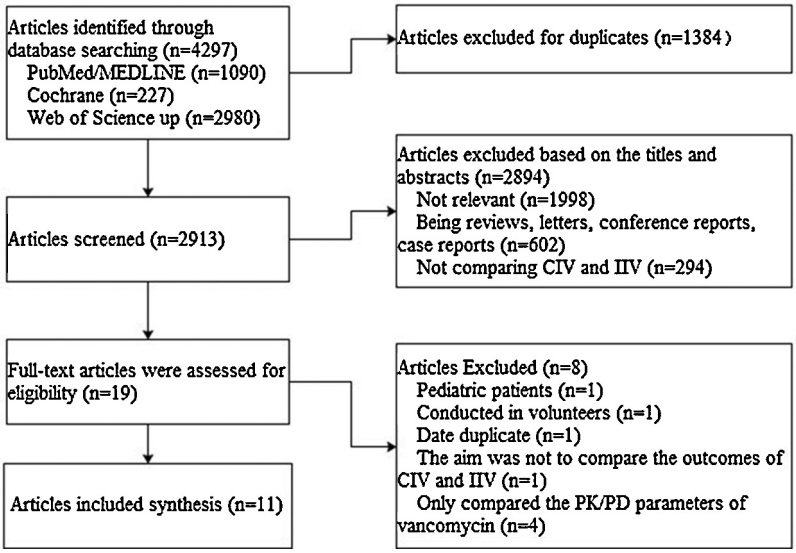

Fig. 1. Flow chart depicting the selection process of studies included in the meta-analysis. CIV, continuous infusion of vancomycin; IIV, intermittent infusion of vancomycin; PK/PD, pharmacokinetic/pharmacodynamic.

2.1. Article identification

PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Library and Web of Science up to June 2015 were searched to identify all papers published in English. The search terms included 'vancomycin', 'intravenous', 'parenteral', 'continuous', 'intermittent', 'discontinuous', 'infusion', 'administration' and 'dosing'. References from relevant articles and reviews were also searched manually to identify additional eligible studies. Considering the small number of randomised controlled trials (RCTs) on this subject, no predefined limitations on study design were applied. RCTs, cohort studies and case-control studies were all included.

2.2. Study selection

Two reviewers (J-JH and HC) searched the literature independently. A study was considered eligible if it met the following criteria: (i) study population was adult patients with a bacterial infection requiring intravenous (i.v.) vancomycin therapy; and (ii) studies compared at least one of the following outcomes of CIV with IIV: mortality, treatment failure, nephrotoxicity or other adverse drug events. Exclusion criteria were: (i) non-i.v. administration of vancomycin; (ii) studies focusing only on pharmacokinetic/pharmacodynamic (PK/PD) parameters; (iii) studies on surgical prophylaxis for infections; (iv) animal experiments; and (v) case reports or case series.

2.3. Quality assessment

The modified Jadad scale [39] was used for quality assessment of RCTs, and the Newcastle–Ottawa quality assessment scale (NOS) [40] was used for quality assessment of non-randomised observational studies. The modified Jadad scale consists of four items regarding details of randomisation, allocation concealment, blinding, and dropouts and withdrawals. The scale ranges from 0 to 7. High-quality RCTs score >4 points, whilst low-quality RCTs score $\leq$4 points. The NOS was developed for cohort and case-control studies and is categorised into three dimensions, including selection, comparability and outcome (cohort studies) or exposure (case-control studies). A rating between zero and nine stars is used for a semi-quantitative assessment of studies, where five or more indicates high quality.

2.4. Data extraction

The following data were extracted from the included studies: year of publication; first author; country; study design; number of patients included in the two groups; patient characteristics [age, body weight, clinical setting, type of infection, pathogens and Simplified Acute Physiology Score (SAPS)]; characteristics of vancomycin administration (loading dose for CIV, dose of vancomycin, target and mean serum vancomycin concentration, time to achieve target serum concentration and duration of treatment); nephrotoxicity; adverse effects; mortality; treatment failure; and PK/PD parameters. Data extraction was performed by J-JH and HC independently. Disagreements were solved by consensus or by discussion with another investigator (J-XZ).

2.5. Outcome variables and definitions

The primary outcomes of this meta-analysis were treatment failure and nephrotoxicity. Treatment failure was defined as clinical, laboratory or radiological parameters not improved or worse after vancomycin therapy. Nephrotoxicity was defined as a serum creatinine increased >0.5 mg/dL or >50% from the baseline value, as a 50% reduction in the calculated creatinine clearance compared with the baseline value, or as a need for renal replacement therapy (RRT). Secondary outcomes included mortality, adverse effects, duration of treatment and serum vancomycin exposure. Overall mortality and infection-related mortality were assessed. Adverse drug events included red man syndrome, allergic reaction, phlebitis and thrombocytopenia, etc. Vancomycin exposure included the mean daily dose of vancomycin, the mean steady-state concentration (C_{ss}) for CIV and the mean trough concentration (C_{min}) for IIV, the time to reach the target serum concentration and the 24-h AUC (AUC_{24}) for both strategies. Data conforming to any outcome definitions reported in each study were used.

2.6. Statistical analysis

Data were analysed using Stata v.12.0 (Stata Statistical Software, College Station, TX). Pooled risk ratios (RRs) and 95% confidence