International Journal of Antimicrobial Agents xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Review

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

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ARTICLE INFO

Article history:
Received 4 May 2015
Accepted 16 October 2015

Keywords:
Vancomycin
Infection
Continuous infusion
Intermittent infusion
Clinical efficacy
Safety

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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http://dx.doi.org/10.1016/j.ijantimicag.2015.10.019
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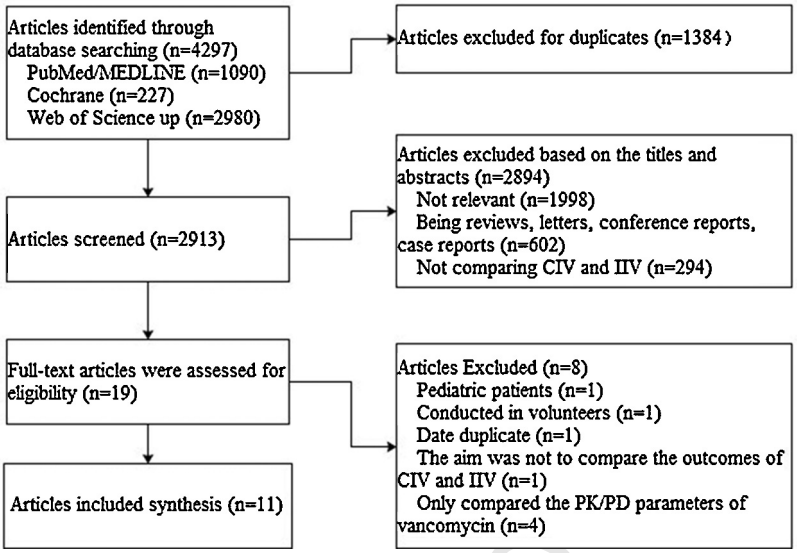

Fig. 1. Flow chart depicting the selection process of studies included in the meta-analysis. CIV, continuous infusion of vancomycin; IIV, intermittent infusion of vancomycin; PK/PD, pharmacokinetic/pharmacodynamic.

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 ≤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

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intervals (CIs) were calculated for dichotomous data. The standardised mean difference (SMD) and 95% CIs were calculated for continuous outcomes. Meta-analysis was done if more than three studies reporting data on the same outcomes were available. Heterogeneity was evaluated by means of the I^2, and a value of >50% was defined to indicate significant heterogeneity. When the heterogeneity was greater than this threshold, possible explanations were investigated using sensitivity analysis.

Publication bias was assessed by the Begg's funnel plot [41]. A fixed-effect model was used when there was mild to moderate heterogeneity between the studies, otherwise a random-effects model was used as appropriate.

3. Results

3.1. Study selection

The selection process of studies included in this meta-analysis is shown in Fig. 1. The initial database search yielded 4297 records, of which 1384 were excluded as duplicates and 2894 were excluded based on the titles and abstracts for various reasons (reviews, letters, conference reports, case reports, not comparing CIV and IIV, or irrelevance to the analysis). The remaining 19 full-text articles [14–32] were assessed for eligibility, 8 of which were also excluded: 1 conducted in paediatric patients [29]; 1 conducted in volunteers [16]; 1 for data duplicate [20]; 1 as the aim was not to compare the outcomes of CIV and IIV [31]; and 4 that only compared the PK/PD parameters of vancomycin [15,19,22,32]. Eleven articles [14,17,18,21,23–28,30] were included eventually, comprising 1299 patients treated with vancomycin (477 by IIV and 822 by CIV).

3.2. Study description

A summary description of the included studies is given in Table 1. The studies spanned from 1995 to 2015. Of the 11 included studies, 2 were RCTs [18,28], 1 was a historical-control study [14] and 8 were cohort studies [17,21,23–27,30]. No case-control study was included in the review. All of the included studies were approved by the local ethics committee. The characteristics of vancomycin administration in all of the studies are shown in Table 2.

3.3. Quality assessment of the included studies

Quality assessment of RCTs was performed using the modified Jadad scale [18,28]. One RCT achieved 5 points [18] and the other achieved 4 points [28]. Non-RCTs were assessed by the NOS [14,17,21,23–27,30]. Five studies were assigned 5 stars [17,23,25,27,30], three studies were assigned seven stars [14,21,24] and one study was assigned six stars [26]. These studies are summarised in Table 3.

3.4. Treatment failure

Four studies reported the incidence of treatment failure [18,21,25,26]. The RCT defined clinical failure including patients who died from the infection, so the number of treatment failures in our study was 7/61 in the CIV group and 4/58 in the IIV group [18]. The incidence of clinical failure was lower in the CIV group than in the IIV group in two studies [21,26], whilst it was higher in the CIV group than in the IIV group in the other two studies [18,25]. However, none of the studies reported a significant difference between the two groups.

Table 1
Characteristics of studies included in the review.

Reference	Design	Setting	Bacteria	No. of patients		SAPS II		SCr (mg/dL)[a]				No. of patients with other antibiotics	
				IIV	CIV	IIV	CIV	IIV1	IIV2	CIV1	CIV2	IIV	CIV
Wysocki et al. [14]	HisC[b]	ICU	MRSA	13	13	13	17	143	158	113	114	NR	NR
Di Filippo et al. [17]	ReC	ICU	MRSA/MRCoNS	14	11	44	50	NR	NR	NR	NR	14 MON/AG	11 MON/AG
Wysocki et al. [18]	RCT	ICU	MRSA	58	61	13	14	88	108	98	120	13 FA; 16 AG	13 FA; 16 AG
Vuagnat et al. [21]	PrC	M/S wards	MRSA/MRCoNS	21	23	NR	NR	85	90	85	90	9 RIF; 2 CIP	5 RIF; 4 CIP
Hutschala et al. [23]	ReC	ICU	Gram-positive	30	119	34	37	90	170	90	150	8 CARB/CEPH; 3 AG	31 CARB/CEPH; 14 AG
Ingram et al. [24]	ReC[c]	OPAT	MRSA/MRCoNS/*Enterococcus* sp.	40	40	NR	NR	NR	NR	NR	NR	NR	NR
Akers et al.	ReC	ICU	*S. aureus*	81	90	NR	NR	97	NR	99	NR	NR	NR
Verrall et al. [26]	ReC	OPAT	MRSA	56	188	NR	NR	NR	NR	NR	NR	2 RIF; 2 CIP	3 RIF; 3 CIP; 2 TRI
Saugel et al. [27]	ReC	ICU	Gram-positive	79	164	NR	NR	NR	NR	NR	NR	NR	NR
Schmelzer et al. [28]	RCT	ICU	NR	36	37	NR	NR	NR	79	NR	72	NR	NR
Tafelski et al. [30]	PrC	ICU	NR	49	76	51	47	NR	NR	NR	NR	NR	NR

AG, aminoglycosides; CARB, carbapenems; CEPH, cephalosporins; CIP, ciprofloxacin; CIV, continuous infusion of vancomycin; FA, fusidic acid; HisC, historical-control study; ICU, intensive care unit; IIV, intermittent infusion of vancomycin; MON, monobactams; MRCoNS, meticillin-resistant coagulase-negative staphylococci; MRSA, meticillin-resistant *Staphylococcus aureus*; M/S, medical/surgical; NR, not reported; OPAT, outpatient parenteral antimicrobial therapy; PrC, prospective cohort study; RCT, randomised controlled study; ReC, retrospective cohort study; RIF, rifampicin; SAPS, Simplified Acute Physiology Score; SCr, serum creatinine; SXT, trimethoprim/sulfamethoxazole.

[a] IIV1 and CIV1, before vancomycin treatment; IIV2 and CIV2, at the end of vancomycin treatment.

[b] Patients receiving CIV were matched with historical patients who received IIV; matching criteria were site of infection, sex, age, body weight, severity of illness, duration of therapy and SCr concentration before vancomycin therapy.

[c] Patients from a cohort study were matched based on the propensity score estimating the probability of being given CIV. Factors used in the propensity score matching process were diabetes mellitus, baseline SCr and MRSA aetiology.

Table 2
Characteristics of vancomycin administration in the studies included in this review.

Reference	Loading dose	Vancomycin dosage		Target vancomycin serum concentration (mg/L)		Duration 1 (h)[a]		Duration 2 (days)[b]		Concentration (mean ± S.D.) (mg/L)	
		IIV	CIV	IIV	CIV	IIV	CIV	IIV	CIV	C_{min}	C_{ss}
Wysocki et al. [14]	15 mg/kg	15 mg/kg b.i.d.	30 mg/kg/day	5–10	20–30	62	55	16	16	6 ± 8	24 ± 6
Di Filippo et al. [17]	500 mg	0.5 g q.i.d.	83 mg/h, 2 g/day	NR	NR	NR	NR	6	6	30 ± 6	24 ± 4
Wysocki et al. [18]	15 mg/kg	15 mg/kg b.i.d.	30 mg/kg/day	10–15	20–25	51	17	14	13	15 ± 9	24 ± 8
Vuagnat et al. [21]	20 mg/kg	20 mg/kg b.i.d.	40 mg/kg/day	20–25	20–25	420	235	66	101	21.7 ± 9.3	26.0 ± 6.1
Hutschala et al. [23]	20 mg/kg	According to target C_{min}[c]	36 mg/kg/day	15	20–25	50	16	9	9	17.0 ± 4.7	25.0 ± 4.0
Ingram et al. [24]	NR	At the discretion of the attending physicians	NR	NR	NR	NR	20	22	9.7 ± 5.0	13.6 ± 6.2	
Akers et al. [25]	1 g	1 g t.i.d.	3 g/day	15–20	20–25	NR	NR	NR	NR	NR	NR
Verrall et al. [26]	NR	NR	NR	15–20	15–25	NR	NR	33	30	NR	NR
Saugel et al. [27]	1 g or 1.25 g	1–2 g daily	60 mg/h or 40 mg/h for patients on RRT	5–10	15–25	NR	NR	7[d]	6[d]	9.1[d]	19.8[d]
Schmelzer et al. [28]	20 mg/kg	15 mg/kg t.i.d.	0.9–2.4 mg/kg/h	15–20	15–25	NR	NR	NR	NR	8.9 ± 3.9	19.8 ± 6.13
Tafelski et al. [30]	1 g	0.5 g q.i.d., 1 g b.i.d.	2 g/day	15–20	15–25	72	96	5[d]	7[d]	NR	NR

b.i.d., twice daily; CIV, continuous infusion of vancomycin; C_{min}, vancomycin trough concentration; C_{ss}, vancomycin steady-state concentration; IIV, intermittent infusion of vancomycin; NR, not reported; q.i.d., four times a day; RRT, renal replacement therapy; S.D., standard deviation; t.i.d., three times a day.

[a] Time to achieve target serum concentration.
[b] Duration of treatment.
[c] The authors did not report a standard dose for IIV but stated that the dosage was adjusted according to serum creatinine concentration and vancomycin concentration.
[d] Median value.

3.5. Nephrotoxicity

Ten studies assessed the incidence of nephrotoxicity [14,17,18,21,23–25,27,28,30]. Only one study reported that the incidence of nephrotoxicity of vancomycin was significantly lower in patients receiving CIV than patients receiving IIV [27], whilst the other studies did not find a statistically significant difference. There was no heterogeneity ($I^2 = 0\%$) and there was a lower incidence of nephrotoxicity in patients treated with CIV compared with patients treated with IIV (RR = 0.61, 95% CI 0.47–0.80; $P < 0.001$) (Fig. 2) after synthesis of the data. In addition, publication bias was not observed ($P = 0.061$).

Three studies reported cases of nephrotoxicity in which RRT was required [18,23,27], only one of which reported that the incidence of nephrotoxicity was lower in the CIV group than that in the IIV group [27].

3.6. Mortality

Seven studies were included in the evaluation of overall mortality [14,17,18,21,23,25,30]. Heterogeneity was not found ($I^2 = 0\%$) and there was no statistically significant difference in the risk of mortality between patients receiving CIV and those receiving IIV (RR = 1.15, 95% CI 0.85–1.54; $P = 0.365$) (Fig. 3), similar to each article. Publication bias was not found ($P = 0.851$).

Only three studies reported mortality due to infection [14,17,18]. Di Filippo et al. reported that no patient died from infection [17]. Wysocki et al. reported that 2/13 in the CIV group and 5/13 in the IIV group died [14]. Wysocki et al. also reported a similar tendency (6/61 in the CIV group and 7/58 in the IIV group) [18]. The difference between groups was not statistically significant in all studies.

3.7. Adverse effects

Five studies analysed adverse effects besides nephrotoxicity [17,18,21,23,25]. Akers et al. reported a high number of onset of thrombocytopenia (16/90 in the CIV group and 11/81 in the IIV group; $P = 0.53$) [25]. In the study conducted by Vuagnat et al. [21], adverse drug effect led to termination of treatment in two patients in the CIV group (with catheter phlebitis) and five patients in the IIV group (including two cases of allergic reaction and one case each of catheter phlebitis, severe neutropenia and severe depression). Red man syndrome was reported in two studies, which was observed only in the IIV group [18,23].

3.8. Duration of treatment

Nine studies were assessable for the duration of treatment [14,17,18,21,23,24,26,27,30]. Two studies were not included in the data synthesis since the duration of treatment was described as median and interquartile range [27,30]. One study reported that there was no significant difference in the duration of vancomycin treatment between the CIV and IIV groups ($P = 0.68$) [27]. The other study reported that the duration of vancomycin therapy was longer in the CIV group than in the IIV group ($P = 0.009$) [30]. Heterogeneity was not found ($I^2 = 0\%$) and pooled data showed that there was no significant difference in the duration of treatment in patients treated with CIV and those treated with IIV (SMD = −0.03, 95% CI −0.20 to 0.13; $P = 0.710$) (Fig. 4). Publication bias was not detected ($P = 0.368$). The duration of treatment obviously varied between the studies due to the severity of infection.

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Table 3
Quality assessment for non-randomised observational studies according to the Newcastle–Ottawa quality assessment scale.

Reference	S1	S2	S3	S4	C1	C2	O1	O2	O3	Total
Wysocki et al. [14]	1	1	1	0	1	1	1	1	0	7
Di Filippo et al. [17]	1	1	1	0	0	0	1	1	0	5
Vuagnat et al. [21]	1	1	1	1	0	0	1	1	1	7
Hutschala et al. [23]	1	1	1	0	0	0	1	1	0	5
Ingram et al. [24]	1	1	1	0	1	1	1	1	0	7
Akers et al. [25]	1	1	1	0	0	0	1	1	0	5
Verrall et al. [26]	1	1	1	0	0	0	1	1	1	6
Saugel et al. [27]	1	1	1	0	0	0	1	1	0	5
Tafelski et al. [30]	1	1	1	1	0	0	1	0	0	5

S, selection; C, comparability; O, outcome.

3.9. Vancomycin exposure

The mean daily administered vancomycin dose adjusted according to the target serum vancomycin concentration was reported in six studies [14,18,21,23,25,27]. Three studies suggested that the mean daily dose was higher in the CIV group than in the IIV group when adjusted to maintain the target serum concentration [14,23,25], whilst one RCT reported that the daily dose given over 10 days of treatment was lower with CIV than with IIV [18], whereas two studies showed no significant difference [21,27]. Data synthesis was not carried out due to the high statistical heterogeneity (I^2 = 65.4%).

Eight studies reported the mean C_{ss} for CIV and the mean C_{min} for IIV [14,17,18,21,23,24,27,28], six of which recorded the target trough or plateau concentration of vancomycin [14,18,21,23,27,28]. In two of these, the mean C_{ss} for CIV was higher than the target plateau vancomycin concentration [21,23]. Also, in two studies the mean C_{min} for IIV was higher than the target trough vancomycin concentration [18,23], and in one study the mean C_{min} for IIV was lower than the target trough concentration [28]. Hutschala et al. showed that both the mean C_{min} and C_{ss} are higher than the target trough or plateau concentration of vancomycin [23].

Five studies reported the time to reach the target serum concentration [14,18,21,23,30]. In two of these, a longer time was needed in the IIV group [18,23]. However, the duration was longer in the CIV group in one study (P = 0.022) [30] and another two studies showed no statistical difference [14,21].

AUC_{24} values were reported in only two studies [18,23]. The mean value for the CIV group was lower than the value for the IIV group in both studies (P = 0.025 and P = 0.002, respectively) and

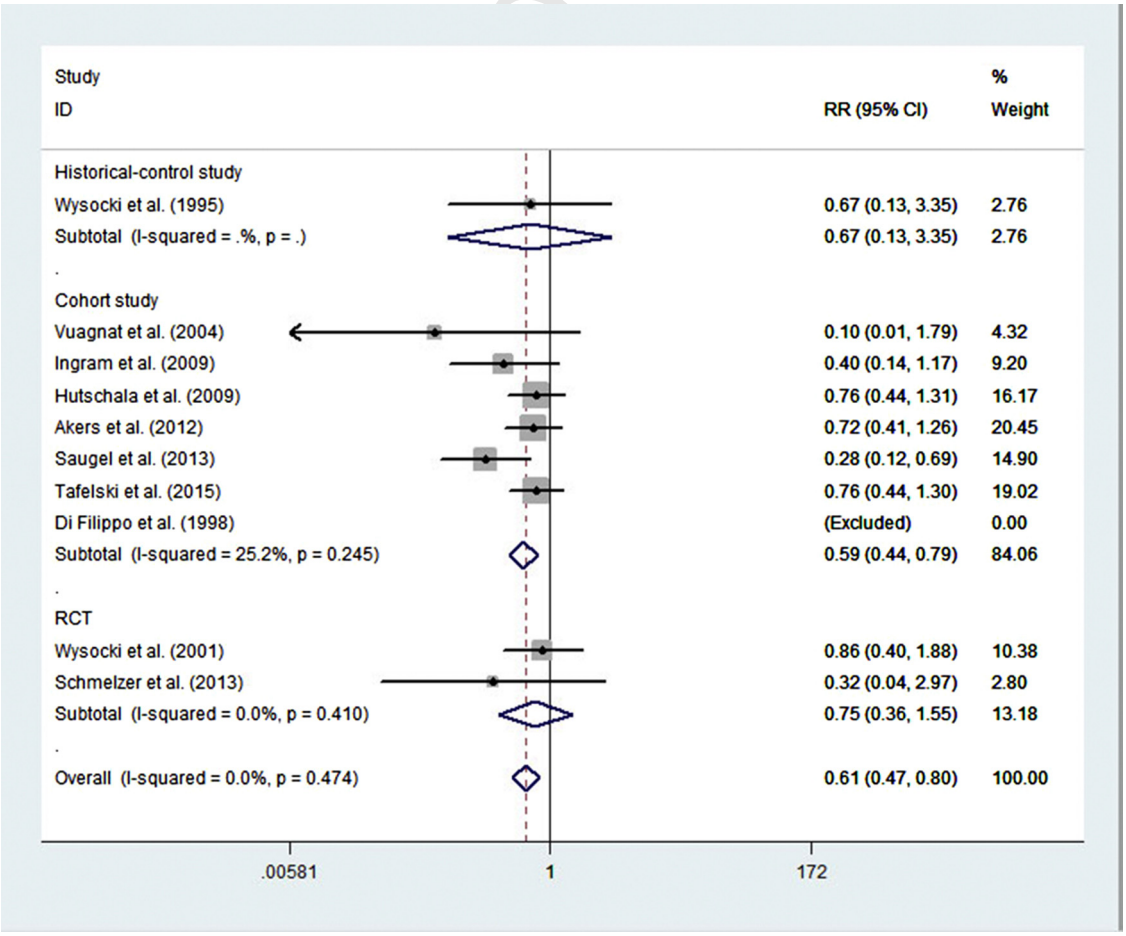

Fig. 2. Forest plot of nephrotoxicity. Forest plot summary of the unadjusted risk ratio (RR) of the studies included in the meta-analysis comparing the incidence of nephrotoxicity in patients treated with continuous infusion of vancomycin (CIV) versus intermittent infusion of vancomycin (IIV). RCT, randomised controlled trial.

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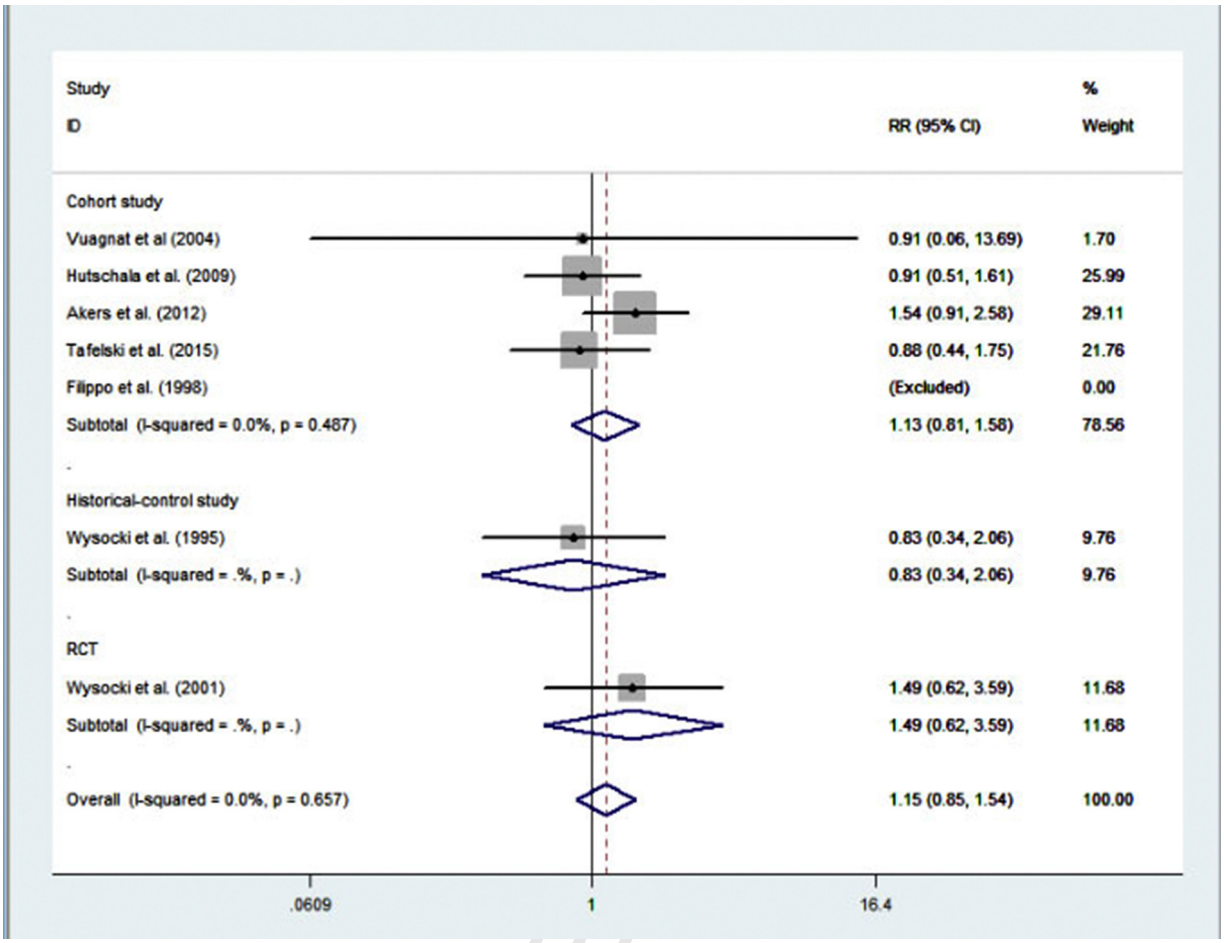

Fig. 3. Forest plot of mortality. Forest plot summary of the unadjusted risk ratio (RR) of the studies included in the meta-analysis comparing overall mortality rates in patients treated with continuous infusion of vancomycin (CIV) versus intermittent infusion of vancomycin (IIV). RCT, randomised controlled trial.

with a lower variability in the CIV group. The $T_{>MIC}$ and AUC_{24}/MIC were not reported in any study.

4. Discussion

In this review, 11 studies published up to June 2015 were enrolled and neither heterogeneity nor publication bias was observed. The meta-analysis showed that CIV had a lower incidence of nephrotoxicity compared with IIV. However, the clinical efficacy was similar; neither treatment failure nor mortality between the two groups was significantly different.

One recently published review comparing the PK/PD parameters showed that CIV was superior to IIV in dosing and monitoring practices [33]. Another two previously published reviews only stated evidence to evaluate the efficacy and safety of different dosing strategies but not integrated the data [35,37] and neither of them supported the routine of CIV.

Compared with the others [34,36,38], the main difference was the number of included articles. We obtained a similar result as the study by Cataldo et al. [34], but van Maarseveen et al. concluded that CIV was as effective as IIV in clinical outcome [36]. There were no differences in the methods or inclusion and exclusion criteria in these two studies, except that five new articles were included. The meta-analysis by Hanrahan et al. [38] demonstrated that CIV had a higher incidence of nephrotoxicity than IIV, which was in contrast to our study. Seven studies were included in their study compared with our eleven articles. Moreover, they also included one article published in 2014 [31] that was not included in our study. The main aim of Hanrahan et al.'s study [31] was to evaluate the relative risk factors for the evolution of acute kidney injury in critically ill patients, and dosing strategy was part of the study. However, the conclusion was in accordance with our summary that CIV is associated with significantly less nephrotoxicity than dosing by IIV. The scarcity of RCTs was the common shortcoming in these three studies, suggesting that a further multicentre RCT is required.

Since the first application of vancomycin several decades ago, its potential for nephrotoxicity has caused considerable controversy [42], and the exact mechanism of nephrotoxicity is not well defined [43]. There are three mechanisms related to nephrotoxicity: (i) the purity of the pharmaceutical preparation; (ii) the severity of disease; and (iii) some parameters related to vancomycin administration (daily dosage, treatment duration and serum concentration of vancomycin etc.). In the current study, we found that nephrotoxicity was significantly lower in CIV compared with IIV. With improved fermentation methods, purity increased from 70% to ca. 95% during the 1990s, which drastically reduced the occurrence rate of nephrotoxicity [44], therefore the purity of the preparation should not be considered. In the present article, five studies compared the severity of diseases in both group and only one showed that the CIV group had a higher severity score [14], with the other four showing an equal severity [17,18,23,30]. This implied that the severity of illness might not relate to the result of the difference in the two administration strategies. Previous studies showed that CIV was proposed to minimise vancomycin serum peak and maximise trough concentrations [13], eliminating the characteristic peak—trough variations of IIV and maintaining a constant C_{ss}

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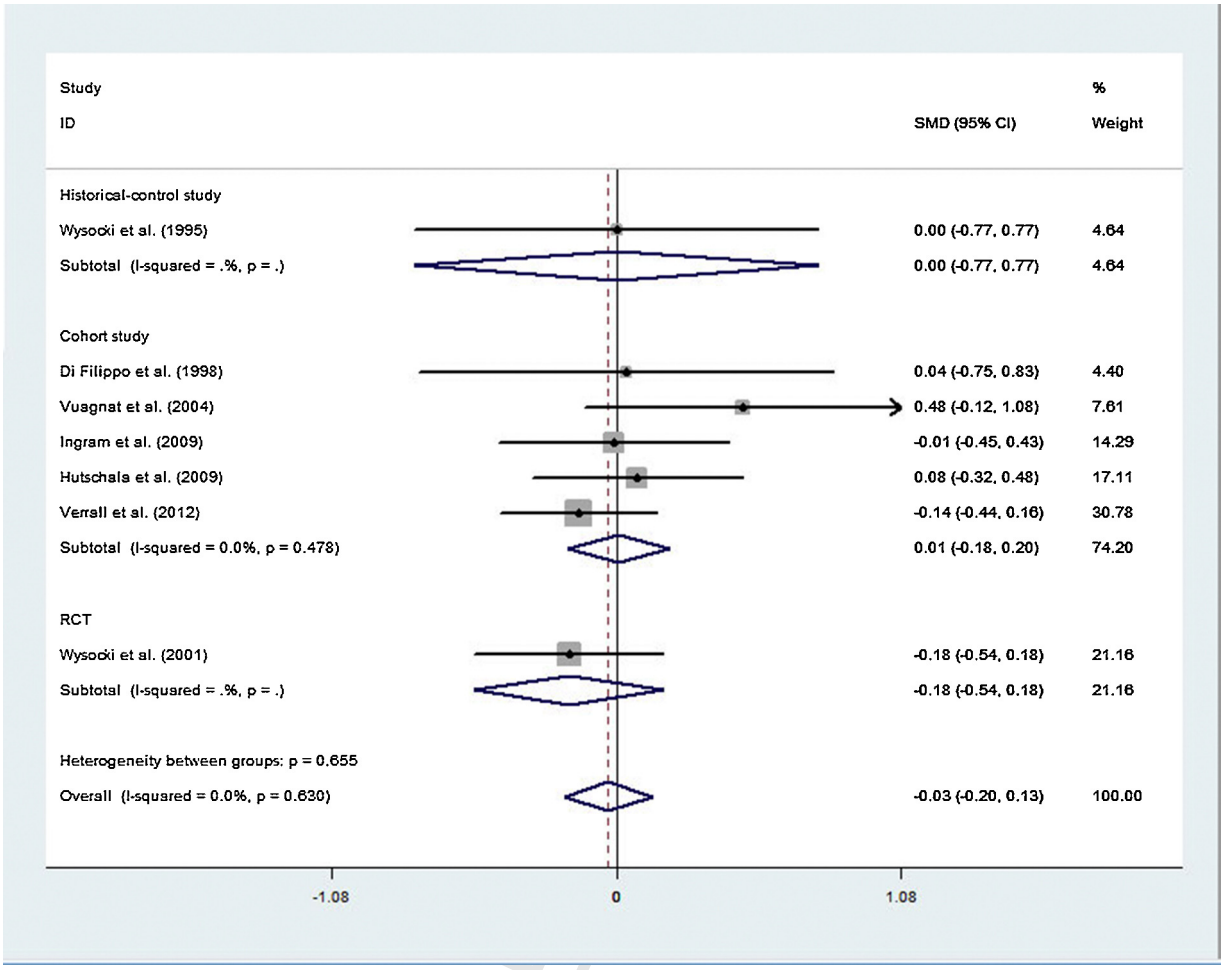

Fig. 4. Forest plot of duration of treatment. Forest plot summary of the unadjusted standardised mean difference (SMD) of the studies included in the meta-analysis comparing the duration of treatment in patients treated with continuous infusion of vancomycin (CIV) versus intermittent infusion of vancomycin (IIV). RCT, randomised controlled trial.

once steady-state was achieved [33]. Moreover, CIV appeared to achieve a safer serum concentration profile when IIV and CIV dosing regimens were adjusted to achieve the same AUC_{24} [34]. These advantages might be the main reasons for the renal protective effect of CIV.

This meta-analysis showed a non-significant difference in clinical efficacy, including mortality and treatment failure, in adult patients with infections treated with CIV versus IIV. First, many factors are associated with the therapeutic efficacy of vancomycin, including general demographic characteristics, primary disease severity, co-morbidities, susceptibility of the causative organism, anatomical site of infection and PD/PK properties etc. [45].

However, none of these conditions were compared in the enrolled studies. Second, treatment failure of antimicrobial therapy was due to the continuous growth of bacteria, which could accelerate the conversion from sepsis to multiple organ failure and even to death [23]. Only two studies reported infection-related mortality and the rate was lower in the CIV group than in the IIV group owing to the shorter time to reach the target concentration [14,18]. Therefore, the similarity of efficiency between CIV and IIV needs further investigation.

There were several limitations that should be considered when interpreting the results. First, among the 11 included studies, only 2 were small RCTs and the other 9 studies were observational studies. Observational studies have a high selection bias and confounding by indication in nature. Second, some important parameters were not compared, such as cost effectiveness, length of hospital stay and the eradication of pathogenic bacteria. Third, as the infection categories, bacteria and population were diverse in this study, we could not confidently conclude that CIV was superior to IIV for a specific infection.

5. Conclusions

This meta-analysis showed that CIV had superior safety compared with IIV, whilst there was no significant difference in clinical efficacy. A further multicentre RCT is required to confirm the results.

Funding

This study was funded by Beijing Municipal Administration of Hospital [ZYLX201502].

Competing interests

None declared.

Ethical approval

Not required.

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