

Clinical outcomes of continuous vs intermittent meropenem infusion for the treatment of sepsis: A systematic review and meta-analysis

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Abstract

The antibiotic meropenem is commonly administered to patients with sepsis and septic shock. The aim of this study was to conduct a meta-analysis to evaluate the clinical efficacy and safety of continuous compared to intermittent meropenem infusion for the treatment of sepsis. Electronic databases such as PubMed, EMBASE, Cochrane Library, and China National Knowledge Infrastructure (CNKI) were researched to collect clinical trials comparing continuous and intermittent infusion of meropenem in patients with sepsis. After data extraction and quality assessment of the included studies, Stata v. 12.0 software (Stata Corporation LLC, College Station, USA) was used for a meta-analysis of mortality, clinical cure, microbiological eradication, and safety. Seven studies with a total of 1,191 participants met the inclusion criteria and were included in the meta-analysis. The meta-analysis showed that continuous meropenem infusion was superior to intermittent infusion in terms of mortality (combined risk ratio (RR) = 0.66, 95% confidence interval (95% CI) = 0.46–0.98, $p = 0.03$), clinical cure rate (combined RR = 1.15, 95% CI = 1.02–1.30, $p = 0.026$) and microbiological eradication (combined RR = 1.20, 95% CI = 1.01–1.42, $p = 0.04$), although it may increase the incidence of some adverse events (AEs). Compared with intermittent dosing, administration of meropenem antibiotics through continuous infusion in patients with sepsis is associated with decreased hospital mortality, increased clinical cure rates and greater microbiological eradication. Further high-quality studies should be conducted to confirm our findings.

Key words: sepsis, meropenem, continuous infusion

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Introduction

Severe infections in critically ill patients are a major burden in the intensive care unit (ICU), with persistently high mortality rates.¹ Optimized antibiotic therapy has been suggested as an intervention likely to improve treatment outcomes for critically ill patients.² However, antibiotic resistance has become a major healthcare problem affecting morbidity and mortality in the clinical setting. Antibacterial drug discovery and development have slowed considerably in recent years.³ With the increase of antibiotic resistance and the decrease of the development of new anti-biological drugs, more research on existing antibiotics is needed. In recent years, the effort to maximize antibiotic activity has led to an interest in optimizing antibiotic dosing using the pharmacokinetic (PK) and pharmacodynamic (PD) principles of antibiotics.⁴

Due to the wide-spectrum activity against variety of Gram-negative and Gram-positive microorganisms, and good penetration of body fluids and tissues, meropenem become a common choice for the treatment of critically ill patients.⁵ Similar to other β -lactam antibiotics, it displays time-dependent bactericidal activity and PK/PD characteristics. The parameter that can best predict antibacterial efficacy is the percentage of the dosing interval that free drug concentrations remain above the minimum inhibitory concentration (MIC) during each dosing interval (referred to as %fT > MIC).^{6,7} The optimal outcome of treatment of critically ill patients is most likely to occur when the PK/PD targets are achieved, which is closely related to the maximum antibiotic activity. A minimum standard for carbapenems is that T > MIC should be maintained at least 40%, and a T > MIC of 100% is associated with significantly better clinical and bacteriological outcomes in patients with serious bacterial infections.^{8,9}

Pharmacokinetic studies in both non-critically ill and critically ill patients have demonstrated that administration of β -lactam antibiotics using continuous infusion results in consistent attainment of drug exposures associated with maximal antibacterial effects.¹⁰ Thus, continuous infusion of meropenem has been suggested to maximize the therapeutic potential in critically ill patients. Recently, the use of continuous administration of meropenem among patients with sepsis has been studied in some trials and indicated greater PK efficacy, bacteriological eradication and clinical cure rates.^{11,12} However, the efficacy and safety information of these clinical studies are not identical. Thus, the goal of our analysis was to evaluate the clinical efficacy and safety of continuous compared to intermittent meropenem infusion for the treatment of sepsis, to provide systematic clinical evidence for antibiotic therapy.

Material and methods

Data sources and literature search

We performed a systematic review and meta-analysis to compare continuous and intermittent infusion of meropenem in patients with sepsis. Two reviewers independently searched the medical literature for relevant clinical trials using the electronic databases of PubMed, Excerpta Medica (EMBASE), Cochrane Library, China National Knowledge Infrastructure (CNKI; www.cnki.net), Chinese Scientific Journals Full Text database (CSJFT), Wanfang Data Knowledge Service Platform (WKSP; www.wanfang-data.com.cn), and Chinese Biomedical Literature Service System (CBMdisc), through August 2018. This was supplemented by searching the reference lists of all retrieved studies, review articles, abstracts, and conference reports. The key words used in this search were: [Meropenem], [Antipseudomonal β -lactams], [Continuous infusion], [Prolonged infusion], [Intermittent infusion], [Short-term intravenous infusion], [Critically ill patients], and [Sepsis]. There were no language restrictions.

Study selection

Clinical trials that met the following criteria were included: 1) randomized, controlled trials (RCTs) or cohort studies; 2) prospective clinical trials of continuous compared to intermittent infusion of meropenem treatment in patients with sepsis; 3) studies with all patients enrolled fulfilling the criteria of sepsis; 4) studies reporting data on mortality, clinical cure, microbiological eradication, as well as adverse events (AEs) etc. Exclusion criteria were the following: 1) repeat studies, abstracts, letters, reviews, editorials, or comments; 2) studies reporting on the comparative outcomes of extended or continuous compared to intermittent but for different meropenem products duration in the 2 arms; 3) case reports and case series including <10 patients; or 4) studies reporting only PK or PD outcomes.

Data extraction and quality assessment

Two review authors independently screened the titles and abstracts of each study. The following information was extracted from each study: the first author, the year of publication, the number of patients enrolled in the study, and the therapeutic regimen and doses, in order to understand the baseline of all the included studies. A modified Jadad scale was used to assess the quality of the included randomized studies. The scores of high-quality studies ranged from 4 to 8, whereas low-quality studies ranged from 0 to 3. For non-randomized studies, the quality was assessed using Newcastle-Ottawa Quality Assessment Scale. Each study was graded as either low quality (0–5) or high quality (6–9). Any disagreements were resolved by the 3rd author.

Statistical analysis

The differences between the continuous compared to intermittent administration of meropenem were assessed using the pooled risk ratio (RR) with 95% confidence intervals (95% CI). The summary RR assessments were conducted using a random- or fixed-effect model. Inter-study heterogeneity was tested using the Q-statistic and quantified using the I^2 statistic. If I^2 was $< 50\%$ ($P_{\text{heterogeneity}} > 0.1$), the Mantel–Haenszel fixed-effect model was used; if not, the random-effect model was used. The sensitivity analyses were performed according to the risk of bias. We assessed publication bias using visual inspection of the funnel plot and Egger's test. All calculations were performed using Stata v. 12.0 software (Stata Corporation LLC, College Station, USA). The level of significance was set at p-value less than 0.05 or 0.01.

Results

Search results

The systematic search of the literature for trials on continuous compared to intermittent meropenem infusion for sepsis therapy produced 108 potentially relevant records from the primary search of databases. Of the studies initially identified, we excluded reports that did not fulfill our inclusion criteria after first screening of the titles and abstracts. Finally, 7 studies^{13–19} were considered eligible for the meta-analysis, including 1 RCT¹⁵ and 6 prospective studies.^{13,14,16–19} A flowchart describing the trial screening and selection procedure is shown in Fig. 1. The 7 selected studies, involving a total of 1,191 patients (continuous

group: 587 patients; intermittent group: 604 patients), were published between 2012 and 2018. The sample sizes of these studies ranged from 20 to 220. The total daily dose of meropenem varied both within and between the individual studies. When reported, the duration of treatment was also a variable (Table 1). The Jadad scores of the 7 studies included in the meta-analysis are also listed in Table 1; the mean Jadad score was 4.23 (range: 3–6), suggesting that the overall study quality was fair.

Statistical analysis of efficacy outcomes

Mortality

Four trials^{13,14,17,18} presented information analyzing mortality. Overall, the meta-analysis showed that continuous infusion of meropenem was associated with a lower mortality rate than intermittent intravenous infusion (484 patients, RR = 0.66, 95% CI = 0.46–0.98, $Z = 2.17$, $p = 0.03$; Fig. 2), suggesting that the risk of death in patients with sepsis treated with continuous infusion of meropenem was 34% lower compared with patients treated with intermittent infusion, using the fixed-effects model (heterogeneity test, $\chi^2 = 1.42$, degrees of freedom (df) = 3 ($p = 0.702$), $I^2 = 0\%$).

Clinical cure rate

The RR of the clinical cure rate was reported in all studies.^{13–19} Pooling the outcomes of the 7 studies showed that there was a significant statistical difference in the clinical cure rates between sepsis patients receiving continuous meropenem infusion and those receiving intermittent infusion (557 patients, RR = 1.15, 95% CI = 1.02–1.30,

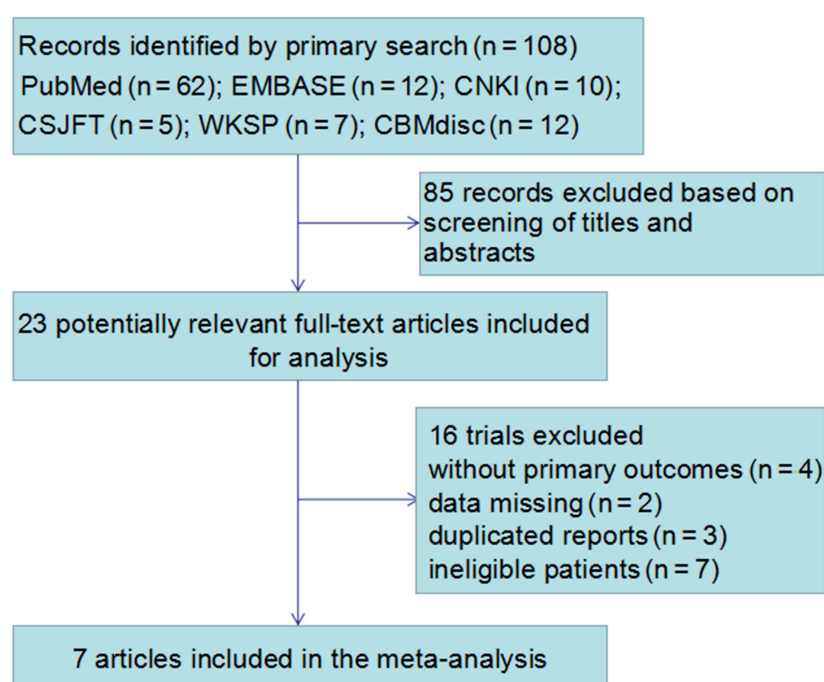


Fig. 1. Flowchart of included and excluded studies

Table 1. Baseline characteristics of the trials included in the meta-analysis

Author	Year	n		Age [years]		APACHE II, SOFA scores (mean \pm SD)	Duration of treatment	Study design	Continuous group	Intermittent group	Jadad score
		CI	IT	CI	IT						
Shabaan et al. ¹³	2017	n = 51 (30/21)	n = 51 (25/26)	NA	NA	NA; NA	up to 7 days	prospective	intravenous infusion of meropenem (20 mg/kg) over 4 h every 8 h	intravenous infusion of meropenem (20 mg/kg) over 30 min every 8 h	5
Zhao et al. ¹⁴	2018	n = 25 (10/15)	n = 25 (11/14)	68.0 \pm 15.4	67.0 \pm 12.2	19.4 \pm 5.0 vs 19.7 \pm 5.9; 8.0 \pm 2.8 vs 8.5 \pm 2.4	median 7 days	prospective	loading dose of 0.5 g of meropenem followed by a continuous infusion of 3 g/day	initial dose of 1.5 g followed by 1 g for every 8 h	4
Dulhunty et al. ¹⁵	2015	n = 212 (130/82)	n = 220 (135/85)	64 (54–72)	65 (53–72)	21 (17–26) vs 20 (16–25); NA	up to 28 days	RCT	loading dose of 3.0 g of meropenem followed by a continuous infusion	loading dose of 3.0 g of meropenem over 30 min followed by intermittent infusion	6
Abdul-Aziz et al. ¹⁶	2016	n = 21 (NA/NA)	n = 21 (NA/NA)	NA	NA	21 (17–26) vs 21 (15–26); 8 (6–10) vs 7 (5–9)	up to 14 days	prospective	loading dose of 1.0 g of meropenem followed by a continuous infusion	loading dose of 1.0 g of meropenem over 30 min followed by intermittent infusion	4
Chytra et al. ¹⁷	2012	n = 120 (78/42)	n = 120 (83/37)	44.9 \pm 17.8	47.2 \pm 16.3	21.4 \pm 7.9 vs 22.1 \pm 8.79; 10.4 \pm 2.9 vs 10.6 \pm 3.5	median 7 days	prospective	loading dose of 2 g of meropenem followed by a continuous infusion of 4 g of meropenem over 24 h	2 g of meropenem over 30 min every 8 h	5
Helmy et al. ¹⁸	2015	n = 50 (33/17)	n = 50 (25/25)	53 (42–61)	55 (40–67)	NA; NA	up to 28 days	prospective	loading dose of 2 g of meropenem intravenously over 30 min followed by continuous infusion of 4 g of meropenem over 24 h	2 g of meropenem over 30 min every 8 h	3
Hassan et al. ¹⁹	2016	n = 108 (NA/NA)	n = 117 (NA/NA)	NA	NA	NA; NA	up to 14 days	prospective	loading dose of 1.0 g of meropenem intravenously over 4 h every 24 h	2 g of meropenem over 30 min every 8 h	3

n – sample size; CI – continuous; IT – intermittent; APACHE II scores – Acute Physiology and Chronic Health Evaluation (Apache) II scores; SOFA scores – Sequential Organ Failure Assessment (SOFA) scores; SD – standard deviation; N/A – not applicable; RCT – randomized controlled trial.

$Z = 2.22$, $p = 0.026$; Fig. 3). Heterogeneity was not observed in the studies ($\chi^2 = 4.62$, $df = 6$ ($p = 0.594$), $I^2 = 0\%$).

Microbiological eradication

Data on comparisons of the microbiological eradication of continuous compared to intermittent intravenous administration of meropenem was reported in 4 trials.^{13,14,17,18} The results of our fixed-effects ($\chi^2 = 3.93$, $df = 3$ ($p = 0.378$), $I^2 = 2.9\%$) meta-analysis for microbiological eradication are summarized in Fig. 4. The results indicated that the microbiological eradication for the continuous group was significantly higher than in the intermittent group (484 patients, $RR = 1.20$, 95% $CI = 1.01$ – 1.42 , $Z = 1.78$, $p = 0.04$; Fig. 4).

Adverse events

Three studies^{13,15,17} provided data regarding AEs that occurred during treatment. In 1 study, out of 212 patients in the continuous group, 39 (18.4%) experienced AEs, compared with 53 of 220 (24.1%) in the intermittent group.¹⁵ Abnormalities in liver and kidney function tests were reported in 1 study, in which 3 out of 51 patients (6%) in the continuous group experienced acute kidney injury, whereas 18 of 12 patients (23.5%) in the intermittent group experienced them.¹³ It has been suggested that gastrointestinal AEs (diarrhea and vomiting) are the most frequent side effects of meropenem in adults, with no significant difference between continuous infusion and intermittent administration (4.2% with diarrhea in the constant group compared to 5.8% in the intermittent group and 1.7% experiencing vomiting in the constant group compared to 2.5% in the intermittent group).¹⁷

Other outcomes of the meta-analysis

Other clinical outcomes of continuous compared to intermittent meropenem infusion for the treatment of sepsis, such as the length of ICU stay, length of hospital stay, ICU survival, ICU-free days, etc., were reported in the included studies and are listed in Table 2.

Publication bias

We assessed publication bias using a funnel plot and Egger's test in this study (Fig. 5). The funnel plot had a certain asymmetry, indicating that

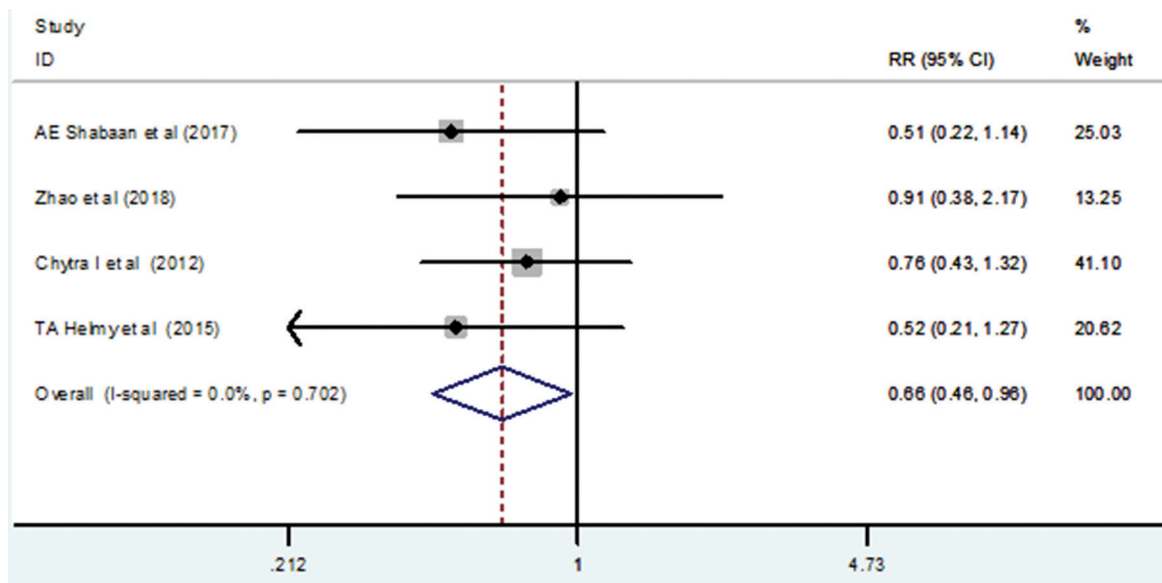


Fig. 2. Forest plot analysis of the mortality rates of continuous compared to intermittent meropenem

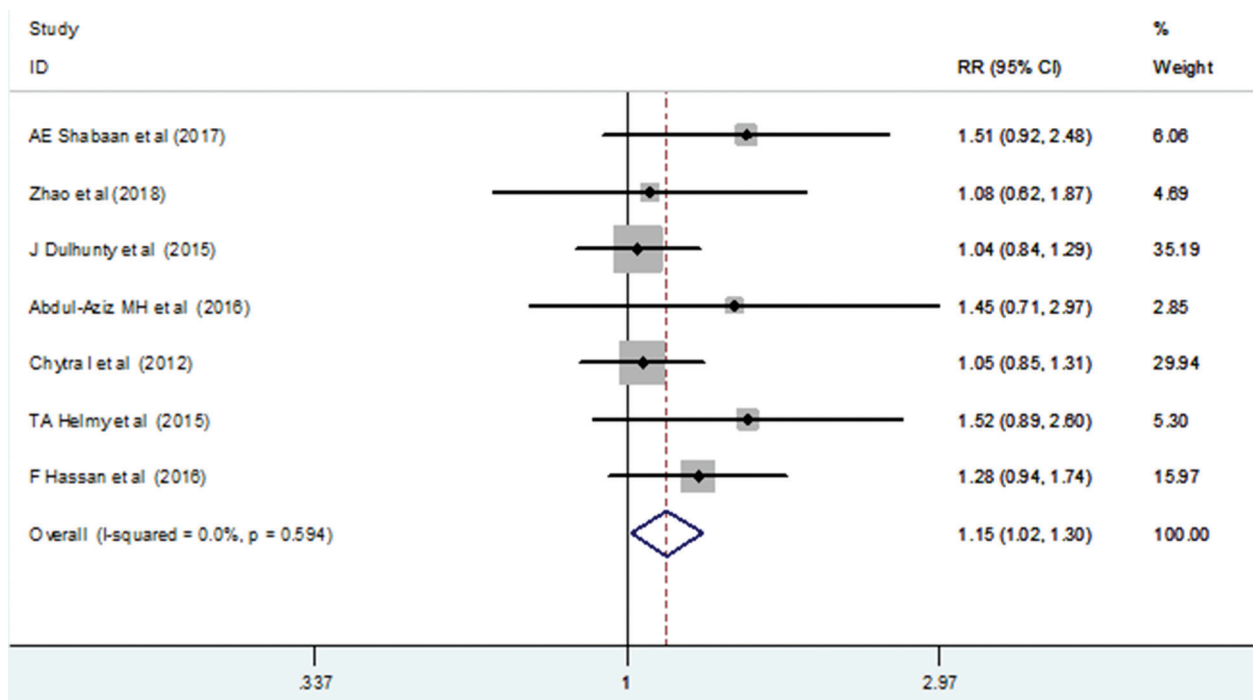


Fig. 3. Forest plots analysis of the clinical cure rates of continuous compared to intermittent meropenem

Table 2. Other outcomes of continuous compared to intermittent meropenem infusion for the treatment of sepsis

Outcomes	Studies	Patients		RR/WMD (95% CI)	Heterogeneity (I ² , P)	p-value
		continuous group	intermittent group			
Length of ICU stay	3	166	166	−1.40 (−2.19, −0.61)	66%; 0.65	0.005
Hospital length of stay	3	288	296	−1.87 (−2.23, −1.50)	41%; 0.18	<0.01
ICU survival	4	378	386	−0.30 (−0.73, 0.13)	0%; 0.54	0.62
ICU-free days	4	378	386	−0.11 (−0.54, 0.32)	12%; 0.57	0.60
Emergence of resistance	2	332	340	−16.23 (−29.86, −2.59)	88%; 0.004	0.02

ICU – intensive care unit.

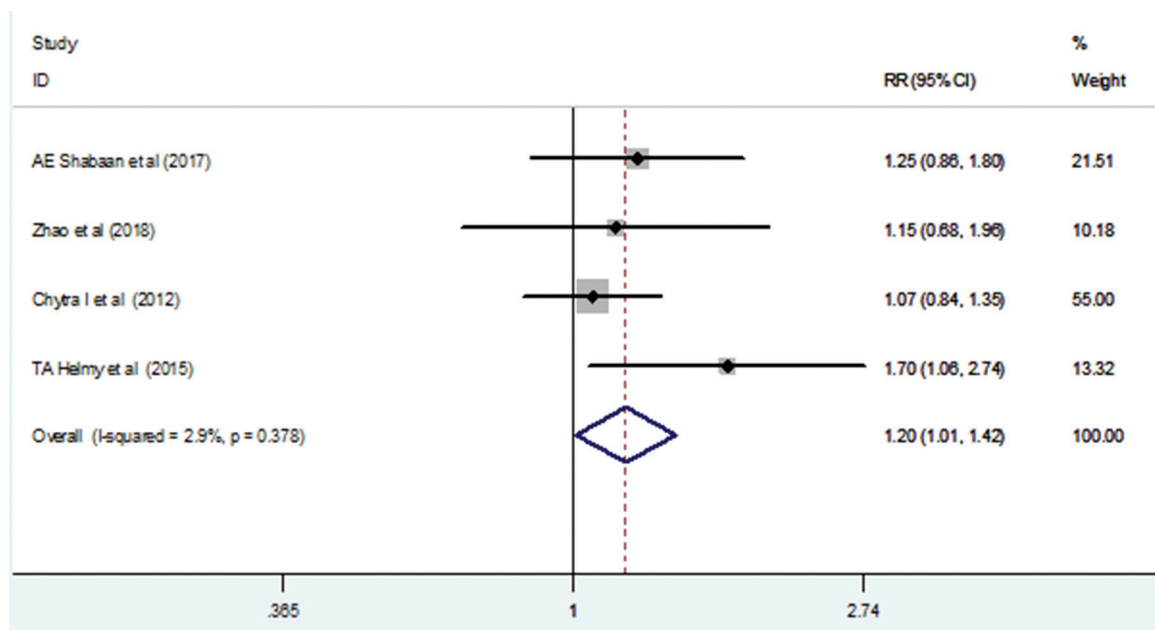


Fig. 4. Forest plot analysis of the microbiological eradication of continuous compared to intermittent meropenem

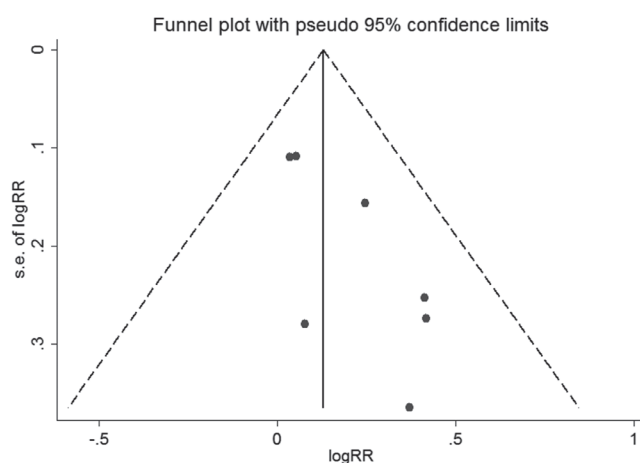


Fig. 5. Funnel plot of publication bias

there is some degree of publication bias in the literature. However, the number of studies included is small, so the funnel plot may not be convincing. Additionally, it was revealed that publication bias was not significant according to Egger's test for the incidence of AEs ($Z = 1.54$; $p = 0.41$).

Discussion

Key findings

To our knowledge, this study is the first meta-analysis to compare outcomes of sepsis patients receiving continuous compared to intermittent intravenous meropenem. In this meta-analysis, which includes data from 1,191 patients, we found that continuous infusion of meropenem resulted in lower mortality than intermittent infusion.

Compared with intermittent infusion, continuous infusion of meropenem was associated with superior clinical cure rates, which is a more subjective outcome.²⁰ Furthermore, a significantly higher rate of microbiological eradication was found in the continuous group compared with the intermittent group, although an insufficient number of patients or studies was included in most of these analyses.²¹ The findings of this meta-analysis suggest that continuous infusion of meropenem could achieve significant clinical improvement in the treatment of sepsis patients.

Relationship to previous studies

Studies of continuous infusion of β -lactam antibiotics, including meropenem, are numerous.²² These studies suggest that continuous infusion achieves a greater likelihood of achieving PK/PD targets than standard intermittent infusion in critically ill patients.²³ However, the clinical value of continuous infusion with meropenem for patients with sepsis has not been systematically analyzed. It has been confirmed that sepsis patients are more likely to have pathophysiological changes leading to sub-therapeutic drug concentrations.^{24,25} A number of PK studies of critically ill patients with sepsis have reported that administration through continuous infusion increases the achievement of target concentrations, both in plasma and in tissues, compared with intermittent dosing.²⁶ More important, previous meta-analyses were less selective than the present analysis in their inclusion criteria, included data from both critically ill and non-critically ill patients, and allowed different β -lactam antibiotics in the 2 treatment groups, which may have diluted any advantage of continuous infusion.²⁷ Our meta-analysis narrowed the subject to sepsis patients and the study drug to meropenem, which could overcome the deficiencies above.

Implications of study findings

Besides the main outcome parameters (clinical cure, mortality and microbiological eradication), there are other factors that differentiate continuous administration from intermittent administration.²⁸ Our results showed that continuous infusion of meropenem could shorten ICU stays and total hospitalization times, which indicates that continuous administration may be a more economical therapy than intermittent administration for sepsis patients.²⁹ Regarding safety, the most commonly reported AEs associated with continuous meropenem infusion included diarrhea, rash, seizures, nausea, and vomiting, as well as hepatic injury.³⁰ Our study implied that administration of meropenem through continuous infusion in sepsis patients was safer compared with intermittent infusion, although the relationship with clinical cure was more complex.

Other considerations

Increasing the % $fT > MIC$ for β -lactams has been associated with increased therapeutic efficacy and delaying the emergence of resistance, and these benefits can be achieved with continuous infusion.^{31,32} However, theoretically speaking, carbapenems such as meropenem may be unsuitable for administration through continuous infusion due to stability issues.³³ Patel et al. showed that 1 mg/mL of meropenem was stable for a longer time than 20 mg/mL and 50 mg/mL at 4–5°C after storage for 3–4 h.³⁴ Tomasello et al. found that there were no statistical differences in the percentage deviation values of the stability profile between concentrations of 4 mg/mL and 10 mg/mL of meropenem after 3–8 h when the temperature was controlled at 25°C.³⁵ Katip et al. demonstrated that 10 mg/mL meropenem solution was stable (maintained more than 90% of its initial concentration) for up to 10 h at 25°C, and that 20 mg/mL meropenem solution was stable for 6 h at 25°C.³⁶ More importantly, meropenem is only stable for 8–12 h at room temperature, thus casting doubts on any potential benefit of continuous delivery.³⁷ This is an important issue in tropical countries where meropenem concentrations decreased by 4% and 12% when stored at room temperature for 3 h and 8 h, respectively, although 24-hour stability can be maintained if meropenem temperature is kept below 4°C.³⁸

Strengths and limitations

There are several limitations in this meta-analysis that should be considered when interpreting the data. First, the number of studies and patients included in this study is small, which will make the conclusion less reliable. Second, differences in treatment regimens and doses of drugs add to the clinical heterogeneity in the data. Third, the criteria used in most trials for the definition and severity of sepsis are not in accordance to the current definitions.

Finally, publication bias might have occurred, and it might not be completely reflected by funnel plot. Therefore, additional large-scale, high-quality, placebo-controlled, double-blind trials are needed to confirm our findings.

Conclusions

The evidence from mainly non-randomized studies suggests that continuous infusion of meropenem could lead to superior treatment outcomes, including mortality, clinical cure, microbiological eradication, and AEs. However, well-designed RCTs are warranted to validate these findings before they can be widely applied in clinical practice.

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