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Original article

Continuous versus Intermittent Use of Meropenem in Septic Critically Ill Patients: A Randomized Controlled Trail

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Abstract

Background: Meropenem is commonly used in the treatment of critically ill patients with sepsis. However, the optimal dosing regimen remains a subject of debate. **This study aimed to** compare the pharmacokinetic, clinical, and bacteriological efficacies of continuous infusion of meropenem versus traditional intermittent administration in critically ill patients with sepsis, and to evaluate the safety of both dosing regimens. **Methods:** This prospective randomized controlled trial was conducted on critically ill patients diagnosed with sepsis and admitted to the ICU. Patients were randomly assigned to either the continuous infusion group (n=30) or the intermittent intravenous group (n=30). Clinical parameters, laboratory data, and clinical outcomes were recorded. Microbiological outcomes, including microbiological eradication and superinfection, were assessed. Pharmacokinetic analysis was performed to evaluate drug concentrations. **Results**: The superinfection rate (requiring other antibiotics) was lower in the continuous group (3.3%) compared to 16.7% in intermittent group. The mean total fluid infusion in the first 24hr was 4190 ml in the continuous group compared to 4336 ml in the intermittent group. The mean length of ICU stay was 10.10 ± 6.12 days in the continuous group compared to 11.60 ± 5.55 days in the intermittent group. A significantly lower mean duration of meropenem treatment (9.93 days) was associated with continuous group compared to 11.53 days in intermittent group. Mortality rate was lower in the continuous group (26.7%) compared to intermittent group (40%). **Conclusion:** Continuous infusion of meropenem demonstrated superior clinical and bacteriological outcomes in critically ill septic patients compared to intermittent administration.

Keywords: Sepsis; Meropenem; Continuous Infusion; Intermittent; Pharmacokinetics; Clinical Outcomes.

Introduction

Sepsis in critically ill patients and increasing antibiotic resistance are major healthcare problems affecting morbidity and mortality in the Intensive Care Units (ICUs) (1). Early initiation of effective antimicrobial treatment is an important component of therapy against sepsis and septic shock (2).

Antibacterial drug discovery and development have slowed considerably in recent years. The number of new antibacterial medicines entering the clinic has been declining and, in view of this fact, new compounds for multi-drug resistant Gram-negative bacilli will unlikely be available for more than 10 years (3). The problems associated with escalating resistance and decreased development of antibiotics with novel mechanisms of action has required more research into existing antibiotics (4).

Increasing antibiotic resistance is a major health-care problem in the ICU, but the discovery and development of suitable antibacterial drugs are slow paced and have become more costly (5).

Meropenem is a carbapenem antibiotic frequently prescribed for the treatment of hospital-acquired infections. For critically ill patients with sepsis or septic shock, early and appropriate antibiotic therapy is recognized as the most important intervention available to clinicians (6). Depending on local susceptibility patterns, meropenem is a suitable choice for this indication because of its very broad spectrum of activity against Gram-negative and -positive organisms (7).

Meropenem is a time-dependent antibiotic, whose antibacterial activity is related to the time for which the free concentration is maintained above the MIC during a dosing interval (f T>MIC). The f T>MIC required for optimal bactericidal activity for carbapenems has been reported to be 40% using in vitro and in vivo animal models.5 Cephalosporins are reported to require 50%–70% f T>MIC and penicillin 50%–60% f T>MIC for maximal bactericidal activity (8).

A significant challenge for critical care physicians is achieving appropriate target site concentrations in critically ill patients with sepsis. Physiological changes associated with the disease process can increase drug volume of distribution (V) and drug clearance leading to low plasma concentrations. Data from critically ill patients with sepsis and septic shock show that this altered physiology can reduce tissue concentrations of antibiotics (9). Given that tissues are the source of many infections, altered dosing that seeks to increase the opportunity for therapeutic concentrations should be considered (10).

For time-dependent antibiotics, continuous infusion has been shown to optimize the attainment of pharmacodynamic targets in plasma.9 However, limited data comparing the tissue pharmacokinetics of intermittent bolus and continuous dosing of β-lactam antibiotics exist (11). A population pharmacokinetic analysis that provides

pharmacokinetic–pharmacodynamic data on different dosing regimens is required to guide dosing in this difficult patient population.

So, the goal of trial is to compare the pharmacokinetic, clinical, and bacteriological efficacies of continuous infusion of meropenem versus traditional intermittent administration in critically ill patients with sepsis, and to evaluate the safety of both dosing regimens.

Patients and methods

The prospective randomized controlled clinical trial included critically ill patients of both sexes, diagnosed with sepsis and admitted to the ICU received meropenem therapy. They were selected from Benha University Hospitals for a period of six months from May 2022 to November 2022, after approval from institutional ethical committee.

An informed written consent was obtained from the patients. Every patient received an explanation of the purpose of the study and had a secret code number. The study was done after being approved by the Research Ethics Committee, Faculty of Medicine, Benha University.

Inclusion criteria were all the critically ill patients of both sexes, diagnosed with sepsis and admitted to the ICU, received meropenem therapy.

Meropenem administration was indicated as empirical therapy for severe infection without a proven pathogen, or as a second-line antibiotic based on microbiological findings. Concomitant antimicrobial therapy was permitted. The diagnosis of sepsis was made in accordance with the ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care (12).

Exclusion criteria were age <18 years, pregnancy, acute or chronic renal failure with a glomerular filtration rate (GFR; calculated with the Cockcroft formula) <50 ml/min, immunodeficiency or taking immunosuppressant medication and allergy to meropenem, and previous application of meropenem in the past 2 weeks.

Patients:

Patients were divided into two groups: Group A (continuous infusion group) (n=30): Patients in this group will receive a loading dose of 0.5 g of meropenem in 100 ml of normal saline i.v. infused over 30 min followed immediately by continuous infusion of 3 g of meropenem over 24 h. Regarding meropenem stability, 0.5 g of meropenem will be continuously infused over 4 h in 50 ml of normal saline (13, 14). **Group B (intermittent intravenous group) (n=30):** Patients in this group will receive the first dose of 1.5 g of meropenem in 100 ml of normal saline infused over 30 min, and then 1 g in 100 ml of normal saline infused over 30 min for every 8 h.

Patients in both groups were treated during their ICU stays by the regular team of ICU physicians and received standard intensive care (the researchers were not involved in the clinical strategy).

Meropenem administration were stopped under the following conditions: further bacterial cultures and MIC testing indicated resistance to meropenem, bacterial cultures and MIC testing indicated increased sensitivity to other narrow-spectrum antibiotics, which could better permeate the infection region (de-escalation of antimicrobial therapy), and significant resolution of clinical symptoms and negative bacterial cultures.

All patients were subjected to the following:

Comprehensive patient data were collected, including demographic information, infection-related details, severity assessment scores, laboratory parameters, clinical parameters, and clinical outcomes. The demographic data included age, sex, BMI, and the ASA Physical Status classification to gauge patients' overall health. Infection-related data comprised the diagnosis, site, and etiology of the infection, along with pathogen identification and MICs when applicable. Severity assessment involved calculating the APACHE II and SOFA scores at the outset of meropenem therapy to evaluate illness severity and organ dysfunction. Laboratory parameters included White Blood Cell (WBC) counts and Procalcitonin (PCT) levels measured at days 1 and 5 of therapy to monitor treatment response. Clinical parameters involved daily recording of body temperature, initial serum creatinine levels for renal function assessment, and tracking total fluid infusion during the first 24 hours of meropenem therapy. Clinical outcomes were assessed by documenting ICU mortality rates and the duration of ICU stays for each patient.

Clinical end points:

The primary end points were clinical and microbiological results of meropenem therapy. persistent or progressing signs and symptoms of infection, or death because of infection. Microbiological outcomes included microbiological eradication and superinfection (which was defined as requiring other antibiotics to target a new Gram-negative bacterial infection). Appropriate routine bacterial cultures (including two sets of blood cultures) were obtained before commencing antimicrobial therapy and were repeated daily if clinical manifestations did not resolve or were exacerbated. Secondary end points included ICU mortality, length of ICU stay (LOS), and duration of meropenem treatment.

Clinical success is defined as complete or partial resolution of temperature, clinical signs and symptoms of infection, and leukocytosis. Clinical failure is defined as the appearance of any of the following (15):

Microbiologic methods: Identification of antimicrobial susceptibility and MIC testing were performed in the clinical microbiology laboratory using the VITEK 2 automated system.

Blood sampling: Two milliliters of blood were collected using an indwelling arterial catheter for each blood sample to

determine plasma meropenem concentrations. In the first dosing period (the first 8 h), samples were collected at 0, 30, 60, 150, 200, 360, and 480 min. In the third dosing period (the first 8 h; steady state), blood samples were acquired in line with an intermittent infusion dose or change of continuous infusion bag at 0, 30, 60, 150, 200, and 480 min. The 200-min time point corresponded to nearly 40% of the dosing interval and was regarded as T40%. Specimens were centrifuged at 3000 rpm for 10 min and then frozen at −20°C for subsequent analysis. All samples were assayed individually within 7 days of collection.

Drug assay: Plasma meropenem concentrations will be measured using an ultra-high-performance liquid chromatography (UPLC)-diode array detector-column switching method with the Shimadzu LC-20A Prominence System. The chromatographic column will be the ACQUITY UPLC® BEH C18 column using the gradient elution method (mobile Phase A and extracting mobile Phase C: methanol-0.05 mol/L K_2HPO_4 5:95, adjusted to a pH of 7; mobile Phase B: methanol). The absorbance wavelength will be 299 nm.

Pharmacokinetic analysis: The pharmacokinetic profile of meropenem in the intermittent group will be individually assessed using the Win Nonlin Professional version 5.0.1 software. A one-compartment model with the first-order elimination will be selected to fit the data. Investigated pharmacokinetic parameters included the Vd and total clearance (CL).

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Statistical analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Armonk, NY, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing unpaired Student's t- test and ANOVA (F) test. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test or Fisher's exact test when appropriate. A two tailed P value < 0.05 was considered statistically significant.

Results

Demographic data and baseline clinical data were illustrated in **Table 1**

According to laboratory assessment of the studied groups, baseline WBC count, procalcitonin and GFR showed no statistically significant difference between the two groups. WBC count and procalcitonin at fifth day of meropenem administration showed significantly lower measurements in continuous group than intermittent group. **Table 2**

Based on bacterial infection source, the most common source was the respiratory tract and nosocomial infections (26.7%) in the continuous group, while nosocomial infection (26.7%) was the commonest source of bacterial infection in the

intermittent group. There was no statistically significant difference between the two groups according to source of infection. The most common bacteria found in both groups were Klebsiella spp. (56.7%) in the continuous group and (46.7%) in the intermittent group. There was no statistically significant difference between the two groups according to bacterial cultures distribution. **Table 3**

In terms of pharmacokinetic data, the comparative first and third dosing periods C-max showed significantly lower levels in continuous group than intermittent group. The first and third dosing periods C-min and CT40% showed significantly higher levels in continuous group than intermittent group. **Figure 1**

The end points in meropenem treatment in the studied groups was improvement of clinical signs in 70% of patients in continuous group compared to 53% of intermittent group. The superinfection rate (requiring other antibiotics) was lower in the continuous group (3.3%) compared to 16.7% in intermittent group. The mean total fluid infusion in the first 24hr was 4190 ml in the continuous group compared to 4336 ml in the intermittent group. The mean length of ICU stay was 10.10 ± 6.12 days in the continuous group compared to 11.60 ± 5.55 days in the intermittent group. A significantly lower mean duration of meropenem treatment (9.93 days) was associated with continuous group compared to 11.53 days in intermittent group. Mortality rate was lower in the continuous group (26.7%) compared to intermittent group (40%). **Table 4**

Table 1: Demographic data and baseline clinical assessment of the studied groups

Variable	Continuous group n=30	Intermittent group n=30	*test*	*p*
Age (years)	54.4 ± 10.58	53.8 ± 10.67	t=0.22	0.827
Gender, n (%)	12 (40%)	13 (43.4%)	X^2=0.069	0.793
	18 (60%)	17 (65.6%)		
Weight (kg)	81.03 ± 7.93	80.43 ± 7.94	t=0.293	0.771
APACHE II	21.49 ± 6.05	22.75 ± 5.62	Z=1.073	0.283
SOFA	10.82 ± 2.73	10.84 ± 3.43	Z=0.362	0.717

t= t student test; X^2=Chi square test; *: Significant ≤0.05.

Table 2: Laboratory assessment of the studied groups

Variable	Continuous group n=30	Intermittent group n=30	*test*	*p*
WBC day 1 (x10^9/L)	13.8 ± 1.53	13.35 ± 3.25	Z=0.286	0.421
WBC day 5 (x10^9/L)	10.53 ± 2.06	10.93 ± 2.26	Z=2.685	0.042*
Procalcitonin day 1 (µg/L)	1.67 ± 1.28	3.94 ± 4.26	Z=0.979	0.327
Procalcitonin day 5 (µg/L)	1.14 ± 1.64	2.24 ± 1.98	Z=3.478	<0.001*
Baseline GFR (ml/min)	83.16 ± 15.46	80.56 ± 15.53	Z=0.966	0.334

Data were expressed as mean ± standard deviation (SD) and median (IQR), Z=Mann-Whitney test; *: Significant ≤0.05

Table 3: Source of bacterial infection distribution in the studied groups

Variable		Continuous group n=30	Intermittent group n=30	*test*	*p*
Source of infection, n (%)	Abdominal	4(13.3%)	4(13.3%)	X^2= 1.067	0.985
	Blood stream	0(0%)	1(3.3%)		
	Central nervous system	2(6.7%)	2(6.7%)		
	Respiratory tract	8(26.7%)	7(23.3%)		
	Soft tissue	3(10%)	3(10%)		
	Urinary system	2(6.7%)	2(6.7%)		
	Nosocomial infection	8(26.7%)	8(26.7%)		
	Not identified	3(10%)	3(10%)		
Bacterial culture susceptible to meropenem	Acinetobacter spp.	2(6.7%)	4(13.3%)	X^2= 1.290	0.982
	Citrobacter spp.	1(3.3%)	1(3.3%)		
	Enterobacter spp.	1(3.3%)	2(6.7%)		
	Escherichia coli	2(6.7%)	2(6.7%)		
	Klebsiella spp.	17(56.7%)	14(46.7%)		
	Pseudomonas aeruginosa	2(6.7%)	2(6.7%)		
	No growth	5(16.7%)	5(16.7%)		

Data were expressed as frequency (%), X^2=Chi-Square test; *: Significant ≤0.05

Table 4: End points of meropenem treatment in the studied groups

Variable	Continuous group n=30	Intermittent group n=30	*test*	*p*
Clinical success	21(70%)	16(53%)	X^2=1.763	0.184
Super infection	1(3.3%)	5(16.7%)	X^2=2.963	0.085
Total fluid infusion in the first 24 h (ml)	4190 ± 869.54	4336.67 ± 864.03	Z=0.809	0.419
Length of ICU stay (day)	10.10 ± 6.12	11.60 ± 5.55	Z=1.320	0.187
Duration of meropenem treatment (day)	9.93 ± 5.33	11.53 ± 2.69	Z=2.348	0.034*
Mortality	8(26.7%)	12(40%)	X^2=1.200	0.412

Data were presented as mean ± standard deviation (SD) and frequency (%), Z=Mann-Whitney test; X^2=Chi-Square test; *: Significant ≤0.05.

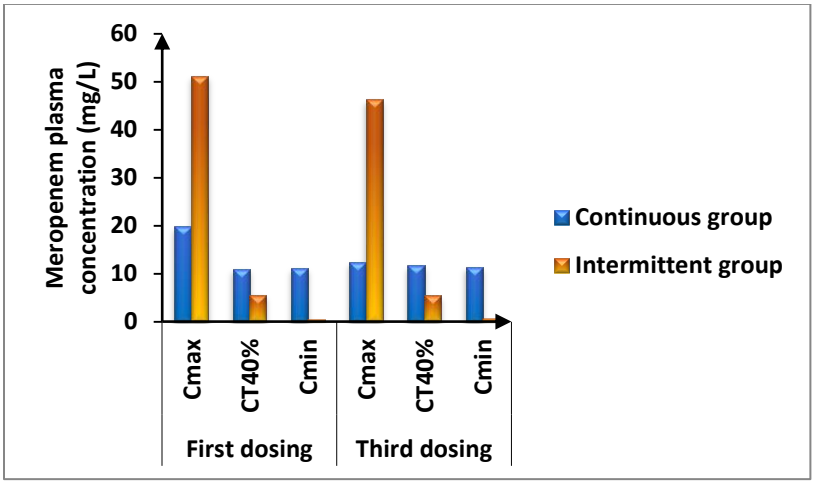

Fig. 1. Plasma concentrations of meropenem administered in both groups first dosing vs third dosing

Discussion

Regarding baseline clinical characteristics, our results are supported by a study revealed that severity of illness (APACHE II and SOFA scores) were insignificantly different between both study groups. The mean APACHE II score in the continuous group was 19.4 ± 5.0, while in the intermittent group it was 19.7 ± 5.9. There was no statistically significant difference between the two groups in terms of APACHE II score (p = 0.523). Similarly, the mean SOFA score in the continuous group was 8.0 ± 2.8, while in the intermittent group it was 8.5 ± 2.4. The difference in SOFA score between the two groups was also not statistically significant (p = 0.577) (16).

In harmony with our findings, a study reported that APACHE II was 21.4 ± 7.9 in the infusion group vs. 22.1 ± 8.79 in the bolus group (P-value = 0.545). Also, SOFA score had a mean value of 10.4 ± 2.9 vs. 10.6 ± 3.5 in the bolus group (P-value = 0.738) (15).

According to laboratory assessment of the studied groups, our study was along with another study which reported that the mean GFR in the continuous group was 97.5 ± 43.4 ml/min, while in the intermittent group it was 91.1 ± 34.0 ml/min. The difference in GFR between the two groups was not statistically significant. For the WBC1 and WBC5 values, the continuous group had a mean WBC1 of 11.5 ± 4.0 × 10^9/L and a mean WBC5 of 9.2 ± 3.9 × 10^9/L, while the intermittent group had a mean WBC1 of 11.9 ± 5.0 × 10^9/L and a mean WBC5 of 10.2 ± 4.3 × 10^9/L. The differences in WBC1 and WBC5 (p = 0.325) between the two groups were not statistically significant. Regarding PCT1 and PCT5 values, the continuous group had a median PCT1 value of 1.3 µg/L and a median PCT5 value of 0.2 µg/L, while the intermittent group had a median PCT1 value of 1.2 µg/L and a median PCT5 value of 0.3 µg/L. The differences in PCT1 and PCT5 between the two groups were not statistically significant (16).

In the present work, according to bacterial infection source, a study to optimize meropenem dosing in patients with severe sepsis/septic shock, their Antimicrobial Stewardship Program implemented an EI meropenem (EIM) protocol in an 18-bed Medical Intensive Care Unit in March 2014. They compared ICU mortality and clinical response in patients who received meropenem for ≥72 hours administered per EIM protocol of 1 g over 3 hours every 8 hours versus intermittent infusion (IIM) protocol of 500 mg over 30 minutes every 6 hours. The IIM protocol group had higher rates of renal dose adjustment at meropenem initiation. Among 56 identified gram-negative (GN) pathogens, 94% had meropenem minimal inhibitory concentration ≤0.25 mg/L (17).

In the current study, the minimum inhibitory concentrations of meropenem was lower in the continuous group (0.36± 0.62 mg/L) than intermittent group (0.47 ± 0.67 mg/L).

In a comprehensive review of 13 randomized controlled trials, **some authors** conducted a comparison between continuous and intermittent infusions of various beta-lactam antibiotics in critically ill adults suffering from respiratory tract infections. Their analysis revealed that in

both groups, most patients consistently met the target of maintaining the concentration of the active drug above the minimum inhibitory concentration (%fT > MIC) during treatment. Notably, the continuous infusion method showed more favorable outcomes, particularly when the offending pathogen's MIC was higher (18).

Consistently, **a study** revealed that the main bacterial MIC in both groups was ≤0.25 (68.2% of the continuous group and 61.9% of the intermittent group); the difference was not significant (16).

In terms of pharmacokinetic data, the comparative first and third dosing periods C-max showed significantly lower levels in continuous group than intermittent group. The first and third dosing periods C-min and CT40% showed significantly higher levels in continuous group than intermittent group.

The importance of optimizing the achievement of pharmacodynamic targets with continuous infusion meropenem appears to be most significant when treating infections caused by Gram-negative bacteria with elevated minimum inhibitory concentrations (MICs) (19).

In another study, Meropenem was administered by CI at a median dose of 6 g over 24 h (IQR 6–6) in 37 patients, and by EII at a median daily dose of 3 g (IQR 2–4), divided into three doses/day (IQR 2–3) administered over 5 hours (IQR 5–5) in 33 patients. Among the patients treated with EII, 21 (64%) achieved the target concentration, whereas 31 (97%) of those treated with CI achieved it (P < 0.001). The median plasma concentration of meropenem was Cmin = 16 mg/L (IQR 8, 23) in the EII group and Css = 34 mg/L (IQR 27, 49) in the CI group (P < 0.001) (20).

Regarding our endpoints, in a meta-analysis of 13 randomized controlled trials, **Lee et al.** compared continuous infusion versus intermittent infusion of various b-lactams in critically ill adult patients with respiratory tract infections and found that continuous infusion significantly improved clinical cure rates, regardless of susceptibility (risk ratio: 1.177; 95% confidence interval: 1.065-1.300) (18).

Conforming our results, **a study** found a nonsignificant difference in cure rates in a trial of 240 critically ill patients randomized to receive meropenem by continuous infusion versus intermittent (bolus) administration (83% vs. 75%, respectively). They showed an improved bacteriological efficacy associated with the continuous application of meropenem and beta-lactams (15).

Regarding the length of ICU and mortality. **In another** study on critically ill patients with sepsis, the researchers compared with intermittent administration, the continuous administration of meropenem did not improve the composite outcome of mortality and emergence of pandrug-resistant or extensively drug-resistant bacteria at day 28 (21).

In consistent with our findings, **a study** reported that the duration of meropenem treatment was significantly shorter in the continuous group (P = 0.035); however, there were no significant differences in other secondary end points including ICU mortality and LOS (16).

In a meta-analysis study, they found no significant differences in cumulative mortality between the two groups (22).

Conclusion

In conclusion, we found that continuous infusion demonstrated superior outcomes. The continuous infusion group exhibited a higher rate of clinical improvement, with a greater resolution of clinical signs compared to the intermittent group. Furthermore, continuous infusion was associated with a lower incidence of superinfection, indicating its potential to prevent secondary infections. Pharmacokinetic analysis revealed differences in drug exposure, with continuous infusion resulting in lower maximum concentration levels but higher minimum concentration levels and concentration at 40% of the dosing interval. Additionally, the continuous infusion group had a shorter duration of meropenem treatment and ICU stay, showing potential benefits in terms of resource utilization and patient management.

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