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Research Article

Comparison of lactate clearance between high-dose and conventional-dose of meropenem in sepsis and septic shock patients at emergency department; post-hoc analysis of a randomized controlled trial

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ABSTRACT

In sepsis and septic shock, patients often face hemodynamic instability, resulting in fluid leakage, heightened capillary permeability, increased distribution volume, and compromised antimicrobial concentrations. Lactate clearance is a well-established marker of illness severity, particularly in the context of sepsis, where it serves as a reliable predictor of mortality. It is notably useful in the determination of resuscitation endpoints. This study aimed to compare lactate clearance within 6 hours between two meropenem dose groups. We conducted a secondary analysis of a randomized controlled trial involving participants aged 18 or older, diagnosed with sepsis and septic shock as per sepsis-3 criteria, and receiving meropenem in an emergency department (ED) setting. The study occurred between December 1, 2017, and August 31, 2018. Of 43 patients, 21 (48.84%) were in the high-dose meropenem group and 22 (51.16%) in the conventional-dose group. Remarkably, a significantly higher proportion of patients in the high-dose group achieved lactate clearance greater than 10% within 6 hours compared to the conventional-dose group (95.2% vs. 63.6%, *P*=0.01). Lactate clearance greater than 10% at 3 days was 85.7% and 86.4% in the high-dose and conventional-dose groups, respectively (*P*=0.95). For 30-day mortality, there were 14.3% and 22.7% in the high-dose and conventional-dose groups, respectively (*P*=0.47). High-dose patients had 18.0 hospital-free days (range 0 to 24) versus 10.0 days (range 0 to 17.0) in the conventional-dose group (*P*=0.17). In summary, this study highlights a higher rate of sepsis and septic shock patients in the high-dose group achieving lactate clearance within 6 hours. This suggests potential benefits linked to the high-dose meropenem regimen for this specific group of patients.

Keywords:
Meropenem, Sepsis, Septic shock, Lactate clearance, Emergency Department

1. INTRODUCTION

Sepsis and septic shock are serious conditions that emerge as a result of the body's response to infections[1]. In Thailand, the frequency of sepsis cases has been steadily increasing. According to data from the Ministry of Public Health and the National Health Security Office, there have been approximately 175,000 cases of bloodstream infections annually, resulting in around 45,000 deaths per year. This places sepsis as the third leading cause of death, following only aging and heart failure. Notably, between 2015 and 2017, the mortality rates for patients with

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community-acquired severe septicemia were recorded at 35.40%, 34.79%, and 32.03% respectively[2].

The Thailand Ministry of Public Health has placed significant emphasis on tackling sepsis, setting specific objectives to decrease the mortality rate among severe sepsis patients admitted to hospitals to below 30% by 2018, and subsequently aiming for a reduction to less than 22% by 2022[2]. This emphasis is particularly directed towards cases of community-acquired sepsis, which necessitate immediate treatment upon arrival at the emergency department (ED). Consequently, prompt identification and effective management of sepsis in the initial hours at the ED have the potential to significantly enhance patient outcome[3-5].

Meropenem remains a favored choice for treating severe infections in critically ill patients[6], and its utility extends to cases of bacteremia and septic shock[7]. However, research by Jaruratanasirikul et al[8] demonstrated that the conventional dose of meropenem (1 g every 8 hours) administered through prolonged infusion in severe sepsis patients was comparatively less effective than a high dose (2 g every 8 hours) with prolonged infusion. This difference was attributed to the altered pharmacokinetics in critically ill patients, including an increase in volume of distribution and a decrease in total body clearance. Notably, the probability of achieving a plasma drug concentration of 80% above the minimum inhibitory concentration (MIC) was only 88.49% in the conventional-dose group, while it rose to 94.72% in the high-dose group[9,10]. These findings emphasize the possible requirement for administering high-dose meropenem to critically ill patients dealing with sepsis and septic shock.

Sepsis patients experience a dysregulated response to infections, where the innate immune system triggers the release of inflammatory cytokines, leading to organ hypo-perfusion, dysfunction, tissue hypoxia, and hyperlactatemia. Clearance of lactate levels has shown promise in reducing mortality rates in the ED. Notably, Bhatet al[11] observed that critically ill sepsis and septic shock patients who achieved lactate clearance within 24 hours in the ED exhibited lower 28-day mortality rates compared to those who did not. Similarly, Filho et al[12] noted that a lactate level exceeding 2.5 mmol/L could predict 28-day mortality among sepsis patients in the ED. Additionally, Junhasavasdikul et al[13] conducted a prospective cohort study at Ramathibodi Hospital's ED, revealing that lactate clearance within 2 hours was a protective factor for sepsis patients requiring ICU admission within 48 hours.

The evidence base indicates that lactate serves as a biomarker of illness severity during physiological stress, particularly in the context of sepsis, where it proves to be a reliable predictor of mortality. Götmaker et al[14] reported that patients with isolated hyperlactatemia exhibited higher 90-day mortality rates compared to those with isolated refractory hypotension. Furthermore, several studies in the literature suggest that assessing lactate changes at the 6-hour mark could guide the treatment of patients with sepsis[15]. Given these insights, our study aims to compare the lactate clearance and other clinical outcomes in critically ill sepsis and septic shock patients receiving high-dose versus conventional-dose meropenem in the ED of a university hospital in Thailand.

While hemodynamic management is pivotal for effective sepsis care, optimal use of antimicrobials equally influences clinical outcomes. Achieving an appropriate antimicrobial dose is crucial for successfully treating sepsis patients with altered pharmacokinetics resulting in decreased drug concentrations. Importantly, there exists a gap in randomized controlled trials investigating the empirical use of high-dose meropenem and its impact on clinical outcomes, including parameters such as lactate clearance, 30-day mortality, and hospital-free days, within an ED setting for sepsis patients. Our primary objective is to evaluate lactate clearance more than 10 percent within 6 hours or normalize lactate at 6 hours among ED sepsis patients treated with high-dose meropenem versus conventional-dose meropenem. Secondary outcomes encompass a comparison of lactate clearance on day 3, 30-day mortality, 30-day hospital-free days, usage of vasopressors, and the occurrence of acute kidney injury (KDIGO stage)[16] between these two treatment regimens.

2. MATERIALS AND METHODS

2.1. Design and setting

We conducted a post-hoc analysis subgroup in an ED of a prospective, single-center, randomized parallel group 1:1, open-label study. The setting was at an ED, supra-tertiaries university hospital, Bangkok Thailand. The randomized controlled trial (RCT) was registered in www.ClinicalTrial.gov identifier NCT03344627[9] and the post-hoc analysis study was registered in Thai Clinical Trial Registry identifier TCTR20200311001. The primary RCT was to compare clinical outcomes between high-dose and conventional-dose meropenem in sepsis and septic shock patients admitted to intensive care unit (ICU) from ED or other hospital wards[10]. Both of studies were approved by the committee on human rights related to research, Faculty of Medicine Ramathibodi Hospital, Mahidol University.

2.2. Selection of participants

2.2.1. Inclusion and exclusion criteria

The inclusion criteria were 1) patients aged ≥18 years, 2) patients diagnosed as sepsis and septic shock regarding sepsis-3 criteria, 3) patients receiving meropenem as an empirical therapy, 4) patients or their legally authorized representative signing informed consent. The exclusion criteria were 1) patients receiving meropenem

within 7 days before the enrollment, 2) patients requiring operations within 72 hours after the enrollment, 3) patients having known allergy or had contraindication to meropenem, 4) patients receiving extracorporeal membrane oxygenation within 3 days after the enrollment, 5) patients with active problems of central nervous system infection, infective endocarditis or osteomyelitis, 6) patients with active seizure or status epilepticus, 7) patients receiving meropenem as an empirical therapy less than 3 days 8) patients with pregnancy and lactation. The patients were enrolled from 1st December 2017 to 31st August 2018.

2.2.2. Randomization allocation and concealment

From the randomized trial, we randomized by using the sealed opaque envelope in a block of four stratified regarding the status of patients before ICU admission (admitted from ED or hospital wards) from http://www.sealedenvelope.com[17].

2.2.3. Data collection and clinical outcomes

Participants were randomized to either high-dose meropenem (the high dose group, 2 g of meropenem intravenous (IV) infused over 30 minutes then 2 g of meropenem IV infused over 3 hours every 8 hours) or conventional-dose meropenem (the standard dose group, 1 g of meropenem IV infused over 30 minutes, then 1 g of meropenem IV infused over 3 hours every 8 hours)[18]. After the first loading dose, the dose of meropenem was adjusted according to creatinine clearance (ClCr) which was calculated by the Cockcroft-Gault formula (Table 1).

The study was an open-label. The both groups of enrolled patients received standard treatment following Ramathibodi Emergency sepsis protocol, ensuring timely administration of antimicrobials within 60 minutes, in accordance with the Surviving Sepsis Campaign guidelines[1]. The researchers had not been involved in other treatments. The combination of antimicrobial, de-escalation, duration of antimicrobial treatment was up to the ED and ICU physician team's decision.

Table 1. Dose adjustment after the first dose of meropenem by creatinine clearance for both arms.

Calculated creatinine clearance	High-dose meropenem	Conventional-dose meropenem
>50 mL/min	2 g every 8 hours	1 g every 8 hours
26-50 mL/min	2 g every 12 hours	1 g every 12 hours
10-25 mL/min	1 g every 12 hours	500 mg every 12 hours
<10 mL/min	1 g every 24 hours	500 mg every 24 hours
Hemodialysis	1 g every 24 hours and 1 g after each dialysis	500 mg every 24 hours and 500 mg after each dialysis

* Calculated creatinine clearance according to the Cockcroft-Gault formula[19].

Baseline characteristics such as age, gender, underlying disease, source of infection, baseline vital sign, initial complete blood count, serum creatinine, serum lactate, SOFA scores were collected at the time of patient enrollment.

Primary outcome was lactate clearance at 6 hours defined by meeting one out of two following criteria: 1) lactate clearance >10% at 6 hours (compare initial lactate level to lactate level at 6 hours after the enrollment), 2) normalized lactate level (lactate level ≥2 mmol/L at 6 hours after the enrollment).

$$\text{Lactate clearance} = \frac{\text{lactate initial - lactate delayed}}{\text{lactate initial}} \times 100$$

Secondary outcomes were: 1) lactate clearance at day 3 defined by meeting one out of two following criteria; lactate clearance >10% at day 3 (compare initial lactate level to lactate level at day 3 after enrollment) or normalized lactate level (lactate level ≥ 2 mmol/L at day 3 after the enrollment), 2) 30-day mortality defined as death from any causes within 30 days after the enrollment, 3) 30-day hospital free day defined as the days that the patients not be in a hospital during 30 days after the enrollment, 4) vasopressor use and 5) acute kidney injury defined by KDIGO[16] stage at day 3 and day 7.

2.2.4. Sample sizes and Statistical Analyses

The sample size was calculated from number of sepsis and septic shock patients who received the conventional-dose meropenem at ED from October to December 2017. Seventy percent of them had lactate clearance within 6 hours. We represented patients who received the high-dose meropenem had lactate clearance at 6 hours for 100%. We apply data to research equation of cohort for binary data. Representing p1 (Exposure)=1.0, p2 (Unexposure)=0.7, ratio (r)=1. Using a 2-side type 1 error= 0.05 power 80%. We need the sample size of 22 participants for each group

We performed intention to treat analysis. We also used descriptive analysis for general characteristic data. For the continuous variables, we presented by mean (standard deviation; SD) in normal distribution or median (interquartile range; IQR) in non-parametric test and using Independent t-test or Mann-Whitney U test as appropriate. For the categorical data, we presented by percentage and using Chi-squared test or Fisher exact test as appropriate. We performed all data analysis by PASW Statistics (SPSS version 18.0).

3. RESULTS

From our randomized trial, a total of 527 patients were screened between December 2017 and August 2018. Among these, 451 patients did not meet the inclusion criteria. Ultimately, 76 participants were included in the randomization process. The remaining 43 patients were enrolled in the Emergency Department, with 21 patients assigned to the high-dose meropenem group and 22 patients to the conventional-dose meropenem group. We excluded 33 participants from the enrollment process outside the Emergency Department, resulting in a total of 43 participants who completed the study (Figure 1).

Baseline characteristics were detailed in Table 2. Overall, 24 patients (55.8%) were male. Age, gender, underlying diseases, and source of infection were generally similar between both groups, except for diabetes mellitus, which was found in 3 patients (14.3%) in the high-dose meropenem group and 10 patients (45.5%) in the conventional-dose meropenem group (*P*=0.03). Vital signs, blood chemistry, serum lactate levels, acute kidney injury (as per KDIGO criteria), SOFA score at enrollment, and microbiological cultures demonstrated no substantial differences between the two groups.

Data following initial interventions, including lactate levels at 6 hours and day 3, SOFA score at day 3, and the delta SOFA score (the difference between mSOFA scores at day 3 after randomization and mSOFA score at day 0 after randomization), were comparable between both groups and did not yield statistically significant differences (Table 2).

Regarding the primary outcome of lactate clearance

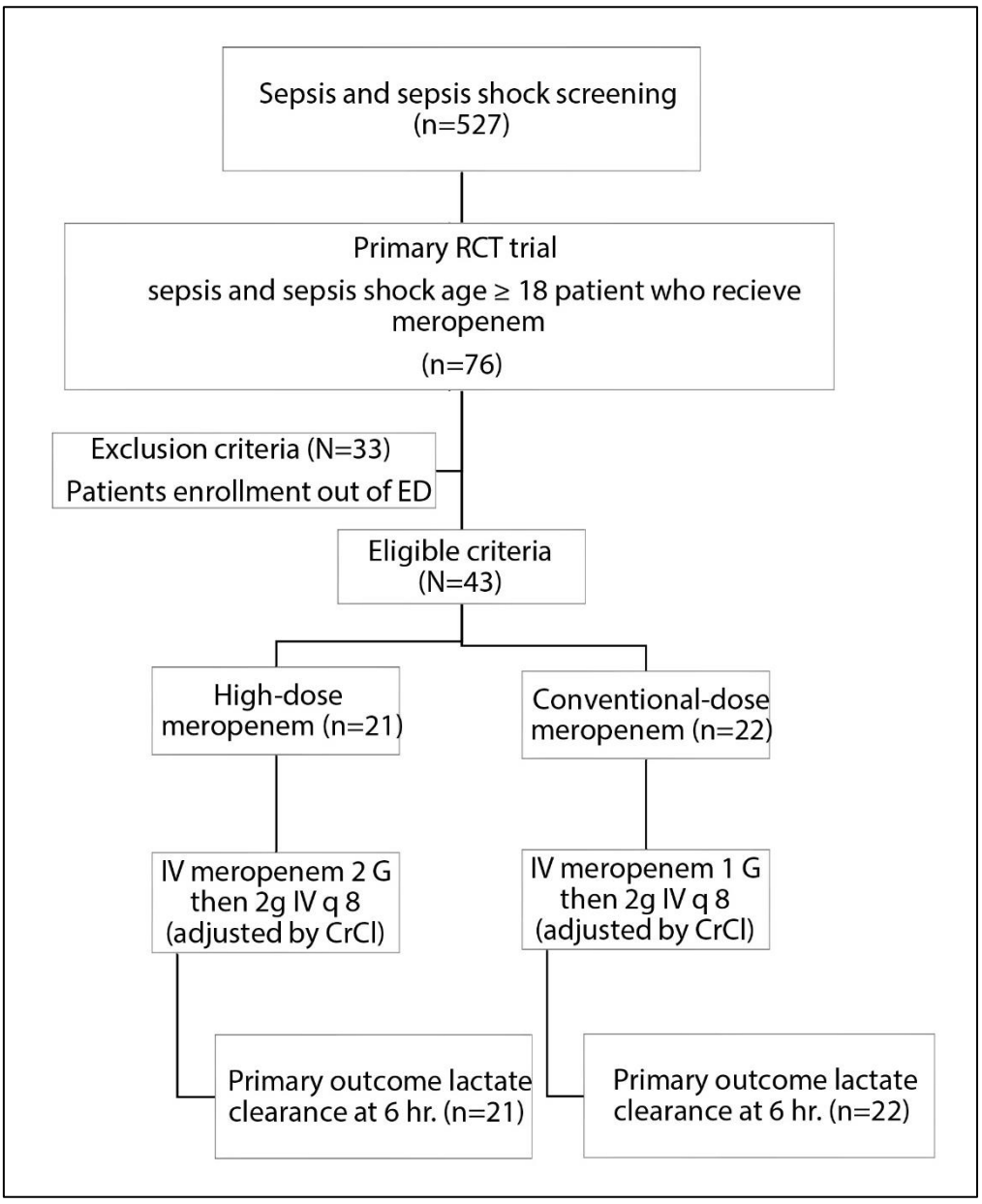

Figure 1. Design and participants flow chart.
CrCl=creatinine clearance, hr=hour

Table 2. Characteristics of participants.

Characteristics	High-dose meropenem (meropenem 2 g) (N = 21)	Conventional-dose (meropenem 1 g) (N = 22)	*P* value
Gender, n (%)			
Male	13 (61.9)	11 (50.0)	0.43
Age (years), Mean (± SD)	69.1 (19.1)	66.8 (14.7)	0.59
Underlying conditions, n (%)			
Hypertension	13 (61.9)	10 (45.5)	0.28
Diabetes mellitus	3 (14.3)	10 (45.5)	0.03
Chronic kidney Disease	7 (33.3)	6 (27.3)	0.67
Heart Disease	6 (28.6)	12 (54.5)	0.08
Liver Disease	1 (4.8)	3 (13.6)	0.32
Immunocompromised	8 (38.1)	12 (54.5)	0.28
Sources of infection, n (%)			0.96
Gastrointestinal	2 (9.5)	0 (0.0)	
Pneumonia	8 (38.1)	11 (50.0)	
Urinary tract	7 (33.3)	8 (36.4)	
Hepatobiliary	1 (4.8)	0 (0.0)	
Systemic	1 (4.8)	0 (0.0)	
Others	2 (9.5)	2 (9.1)	
Vital signs at time of enrollment, Mean (± SD)			
Mean Systolic BP (mmHg)	114.0 (36.1)	118.6 (33.3)	0.67
Mean Diastolic BP (mmHg)	63.7 (15.4)	67.1 (18.4)	0.51
Mean Heart Rate (bpm)	106.6 (26.1)	96.0 (25.7)	0.19
Mean Body Temperature (°C)	38.0 (1.2)	38.1 (1.2)	0.79
Blood chemistry at time of enrollment, Median [IQR]			
White Blood Cell Count	14,400 [770, 16900]	12,000 [6125, 14725]	0.17
Platelet Count	177,000 [77000, 232750]	161,500 [61250, 214750]	0.19
Serum Creatinine	2.0 [2.0, 2.0]	1.0 [0.8, 2.5]	0.30
Serum lactate initial (day 0)	3.2 [1.8, 6.8]	3.1 [1.9, 4.3]	0.83
Acute kidney injury at day 0, n (%)			0.15
No AKI	9 (42.9)	16 (72.7)	
KDIGO 1	4 (19.0)	1 (4.5)	
KDIGO 2	2 (9.5)	1 (4.5)	
KDIGO 3	6 (28.6)	4 (18.2)	
SOFA score day 0, Median [IQR]	6 [3, 9]	6 [2, 8]	0.92
Data after Intervention			
Serum Lactate (mmol/L), Median [IQR]			
At 6 hours	3.0 [1.2, 4.2]	2.5 [1.7, 4.6]	0.92
At 3 days	2.1 [1.9, 2.9]	1.3 [1.1, 2.4]	0.08
SOFA score day 3, Median [IQR]	4 [2.0, 6.5]	5.5 [3.0, 9.0]	0.36
Delta SOFA score (day 3 to day 0), Median [IQR]	0 [-1.5, 1.0]	0 [-1.25, 2.0]	0.38
Microbiological culture, n (%)			0.82
No growth	15 (71.4)	16 (72.7)	
Escherichia coli spp.	2 (9.5)	0 (0.0)	
ESBL-producing *Escherichia coli*	1 (4.8)	4 (18.2)	
Klebsiella pneumoniae	2 (9.5)	0 (0.0)	
Pseudomonas spp.	0 (0.0)	1 (4.5)	
Salmonella spp.	1 (4.8)	0 (0.0)	
Staphylococcus aureus	0 (0.0)	1 (4.5)	

greater than 10% or normalization at 6 hours, the high-dose group (20 patients, 95.2%) displayed significantly better results than the conventional-dose group (14 patients, 63.6%) (*P*=0.01) (Table 3). Specifically, 19 patients (90.5%) in the high-dose group achieved lactate clearance greater than 10%, compared to 14 patients (63.6%) in the conventional-dose group, with a statistically significant difference (*P*=0.04). The rates of lactate normalization at 6 hours were comparable between the two groups (10 patients, 47.6% for high-dose and 7 patients, 31.8% for conventional-dose, *P*=0.29).

For the secondary outcomes, including 30-day mortality, hospital-free days within a 30-day period, vasopressor usage, acute kidney injury on day 3 and day 7 (according to KDIGO criteria), and delta lactate clearance at 6 hours, no significant differences were observed between the two groups. There were no discernible variations in adverse effects such as drug allergies and phlebitis between the high-dose and conventional-dose groups.

Table 3. Primary and secondary Outcomes.

Study outcomes	High-dose meropenem (meropenem 2 g) (N = 21)	Conventional-dose (meropenem 1 g) (N = 22)	*P* value
Primary outcomes, n (%)			
Total outcome of Clearance or normalize lactate at 6 hours	20 (95.2)	14 (63.6)	0.01
Lactate clearance >10% at 6 hours	19 (90.5)	14 (63.6)	0.04
Normalize lactate at 6 hours	10 (47.6)	7 (31.8)	0.29
Total outcome of Clearance or normalized lactate at day 3	18 (85.7)	19 (86.4)	0.95
Lactate clearance >10% at day 3	16 (76.2)	19 (86.4)	0.39
Normalize lactate at 3 day	12 (57.1)	18 (81.8)	0.08
Secondary outcomes			
30-day mortality, n (%)	3 (14.3)	5 (22.7)	0.47
30-day hospital free-day, Median [IQR]	18 [0, 24.0]	10 [0, 17.0]	0.17
Vasopressor use, n (%)	7 (33.3)	13 (59.1)	0.09
Acute kidney injury at day 3, n (%)			0.82
No AKI	12 (57.1)	12 (54.5)	
KDIGO 1	2 (9.5)	1 (4.5)	
KDIGO 2	2 (9.5)	4 (18.2)	
KDIGO 3	5 (23.8)	5 (22.7)	
Acute kidney injury at day 7, n (%)			0.78
No AKI	15 (71.4)	13 (59.1)	
KDIGO 1	1 (4.8)	4 (18.2)	
KDIGO 2	1 (4.8)	1 (4.5)	
KDIGO 3	4 (19)	4 (18.2)	
Delta lactate clearance at 6 hours [a] (%), Median [IQR]	38.9 [20.0, 84.3]	22.6 [16.4, 51.9]	0.10

[a] Delta lactate clearance at 6 hours = (lactate initial-lactate at 6 hours) / lactate initial

4. DISCUSSION

Our prior investigation marked the initial RCT that examined the effects of high-dose meropenem on clinical outcomes, with a specific focus on modified sequential organ failure assessment (mSOFA) scores[10]. Nonetheless, the administration of high-dose meropenem did not yield improved clinical outcomes among individuals with sepsis and septic shock. In a post-hoc analysis, we undertook a subgroup evaluation within the ED, comparing the overall outcomes of lactate clearance or the normalization of serum lactate levels between high-dose and conventional-dose meropenem.

Zhiqiang et al. [20] highlighted serum lactate levels as an autonomous prognostic indicator of mortality in sepsis patients with similar to the SOFA score. Reports by Nguyen et al and Seung et al demonstrated that follow-up serum lactate levels and a clearance exceeding 10% within 2 to 6 hours served as predictors of mortality among sepsis patients in the ED.

Optimizing antimicrobial treatment was another pivotal factor in the care of sepsis patients. This encompassed appropriate antimicrobial loading doses, utilization of highly bactericidal agents, and optimization of antimicrobial pharmacokinetics. The increased volume of distribution (Vd) observed in septic patients leads to a reduction in plasma drug concentrations, especially hydrophilic antimicrobials such as Meropenem. The administration of fluid resuscitation and vasopressors results in a prompt elevation in cardiac output and an augmentation of renal blood flow, thereby enhancing the renal clearance of Meropenem in early stage[21]. Conventional dosing of Meropenem in critically ill septic individuals may not attain the desired pharmacokinetic/pharmacodynamic (PK/PD) targets. Our RCT revealed that the PD target of maintaining drug concentrations above the minimum inhibitory concentration (MIC) at all times was achieved in only 25.0% of cases in the conventional-dose group, whereas the high-dose group achieved a 100% success rate. Boonpeng et al. reported that critically ill patients who achieved a high PD target exceeding the MIC at all times showed favorable survival outcomes[22].

Our study aim to explore the results of lactate clearance in ED sepsis patients who were treated with either high-dose or conventional-dose meropenem. Our main focus was on comparing how well serum lactate was cleared between these two treatment arms. Interestingly, we found a significant difference only when lactate clearance exceeded 10% within the first 6 hours. However, we didn't observe a notable normalization of lactate levels within the same time frame. This could be due to the fact that both groups achieved similar levels of serum lactate normalization after the initial 6 hours, possibly indicating successful hemodynamic resuscitation in both cases. Additionally, by the end of the third day (72 hours), the absolute serum lactate levels had nearly normalized in both groups.

Our results reveal a difference in lactate clearance at 6 hours, and although this discrepancy did not significantly on clinical outcomes. This observation may be influenced

by multiple factors, including increased lactate levels and a concurrent decrease in lactate clearance which we limited the data. However, Jean-Louis Vincent et al. proposed that lactate measurements every 1-2 hours should be employed in acute conditions. Additional research is warranted to explore the utilization of lactate clearance as an endpoint for resuscitation. Moreover, other parameters such as central venous oxygen, central venous-arterial pCO2 gradient (Pcv-aCO2), and peripheral perfusion merit consideration in the context of resuscitation endpoints[23].

In terms of the secondary outcome, the high-dose meropenem group exhibited a seemingly lower 30-day mortality rate compared to the low-dose meropenem group (14.3% vs. 22.7%, respectively, *P*=0.47). Notably, the severity of both groups, as indicated by mSOFA scores 6, appeared similar. Drawing a parallel to data from Lie et al.[24], the 28-day mortality rate was 25% among patients with SOFA scores ranging from 5 to 6, whereas our study found a 22.7% mortality rate in the conventional-dose meropenem group.

However, among patients in the high-dose meropenem group with an mSOFA score of 6, the 30-day mortality rate was as low as 14.3%. If the study were conducted with a larger sample size, the high-dose meropenem group might potentially demonstrate a notable mortality advantage similar to the benefits seen with lactate clearance. Similarly, the high-dose meropenem group demonstrated improved clinical outcomes, including 30-day hospital-free days and the percentage of delta lactate clearance at 6 hours.

Comparing these results with our previously reported data[10], encompassing critically ill patients admitted from both inpatient wards and the ED to the ICU, the 28-day mortality rate was more favorable in the high-dose meropenem group (34.2% vs. 44.7%, respectively, *P*=0.48). However, the present study revealed lower mortality outcomes for critically ill patients admitted from the ED (14.3%) compared to those in the high-dose meropenem group, encompassing both inpatient wards and the ED.

Limitations of our study need to be acknowledged. First, our data was originated from a single center with a relatively small sample size. The reduced sample size might have been influenced by emergency physicians choosing alternative empirical antimicrobials like piperacillin/tazobactam or third/fourth-generation cephalosporins over meropenem. A larger sample size might have yielded different and potentially statistically significant other clinical outcomes.

Secondly, the current Surviving Sepsis Campaign guidelines have not stated a standardized time frame for lactate clearance or a recommended cutoff value for resuscitation targets. Consequently, this absence of guidance may introduce confounding variables, including fluid therapy, treatment timing, and source control, which could complicate the assessment of the relation between lactate clearance and sepsis mortality. Lastly, our ED sepsis protocol was adhered to by approximately 80% of the participants. Recognizing the potential effects of higher adherence on patient outcomes is significant. For a more comprehensive understanding, future research could incorporate additional data on protocol adherence, concurrent therapies, and the timing of interventions.

5. CONCLUSION

In conclusion, our study highlighted that in sepsis patients presenting to the ED, the high-dose meropenem group exhibited superior outcomes in terms of lactate clearance greater than 10% in 6 hours or normalization at 6 hours compared to the conventional-dose meropenem group. Additionally, the high-dose meropenem group showed a favorable trend towards improved 30-day mortality rates and hospital-free days within the 30-day period.

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Conflict of interest
None to declare.

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None to declare.

Ethics approval
This study was approved by the ethics committee of Faculty of Medicine Ramathibodi hospital Mahidol University (COA MURA2017/488 Date of main title approval 21 August 2017, Date of subtitle approval 14 March 2019).

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Author contribution
PS, VT and PD2 designed this study and protocol development. PD1 and TL were responsible for the data collection. PS, PD1, TL and PD2 were responsible for data analysis. PS, PD1, PD2 and PM conducted the manuscript writing. PS, PD2 and PM provided final approval for this version to be published. All authors agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript. Please specify the contribution of each author of your manuscript.

Trial registration

The randomized controlled trial (RCT) was registered in www.ClinicalTrial.gov identifier NCT03344627 and this secondary analysis study was registered in Thai Clinical Trial Registry identifier TCTR20200311001, registered 10 March 2020 - retrospectively registered.

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