Original Article

Efficacy and Safety of Prolonged versus Intermittent Infusion of Beta-Lactam Antibiotics as Empirical Therapy in Patients with Sepsis

Hemvimon S, MD[1], Srinithiwat P, MD[2], Koomanachai P, MD[3], Thamlikitkul V, MD[3], Jitmuang A, MD[3]

[1] Department of Medicine, Saraburi Hospital, Saraburi, Thailand

[2] Department of Medicine, Panyananthaphikkhu Chonprathan Medical Center, Faculty of Medicine, Srinakharinwirot University, Nonthaburi, Thailand

[3] Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Objective: To determine the efficacy and safety of beta-lactam antibiotics (ceftazidime, cefepime, piperacillin/tazobactam, imipenem, meropenem, and doripenem) administered by intermittent infusion (II) compared with three to four-hour prolonged infusion (PI) in acutely ill-hospitalized patients with sepsis.

Materials and Methods: The authors conducted a prospective cohort study between January 2010 and December 2013.

Results: Of 219 subjects, 213 were recruited in the present study, 109 patients were in the II group and 104 patients were in the PI group. No significant difference of baseline characteristics between both groups. About 70% of infections from both groups were associated with hospital-associated infection. Sepsis was significantly higher in PI group (p=0.02). Pneumonia, bacteremia, and urinary tract infection (UTI) were the major foci of sepsis in the present study. *Escherichia coli* that mainly came from UTI was the major etiologic pathogen, whereas the causative pathogen was unknown in 49.3%. The 28-day survival was 87.2% in the II group and 79.8% in the PI group (p=0.27). Favorable clinical outcomes resulted in 74.3% of the II group and 76.9% of the PI group (p=0.11). A complete microbiological response was documented in 62.3% of the II group and 63.2% of the PI group (p=0.91). No serious adverse events were observed in either group.

Conclusion: There were no significant differences in clinical, microbiological, and safety outcomes between the two groups.

Keywords: Beta-lactam antibiotics, Prolonged infusion, Intermittent infusion, Sepsis

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Sepsis is an urgent medical problem associated with high mortality[1]. Early administration of appropriate antimicrobial agents, an optimal dosing regimen, and good supportive therapy can improve clinical outcomes and reduce the emergence of drug-resistant organisms[2-4]. Beta-lactam antibiotics are commonly chosen as the empirical antimicrobial agents in sepsis due to their wide spectrum of activity and tolerability. The principle pharmacodynamic parameter that predicts in vivo efficacy of beta-lactam antibiotics is the duration of the plasma drug concentration maintained above the minimum inhibitory concentration (T>MIC). T>MIC should be maintained during at least 40% to 60% of the interval between doses for susceptible bacteria, and during at least 90% of the dose interval to prevent resistant organisms[5,6]. Continuous or prolonged infusion (PI) of beta-lactam antibiotics has been reported to be more cost effective than intermittent infusion (II) by enhancing their time-dependent activities[7-15]. However, a recent meta-analysis of clinical trials did not demonstrate a difference in clinical cure or survival[9]. Most of these studies were conducted in patients with a single site of infection or one type of organism, not acutely ill patients with sepsis. The aim of the present study was to compare 28-day survival,

Correspondence to:

Jitmuang A.

Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, 2 Wang Lang Road, Bangkoknoi, Bangkok 10700, Thailand.

Phone: +66-2-4197783

Email: anupopmix@yahoo.co.th

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clinical, and safety outcomes, and microbiological response between PI and II of beta-lactams as empirical therapy for patients with sepsis.

Materials and Methods

A prospective cohort study was conducted at the Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University between January 2010 and December 2013. The Scientific and Ethics Committee of the Siriraj Institutional Review Board (SIRB) approved the study.

Patients were eligible for enrollment in the present study if they were 18 years of age or older, admitted to hospital with a clinical suspicion of sepsis and received empirical intravenous beta-lactam antibiotics (ceftazidime, cefepime, piperacillin/tazobactam, imipenem, meropenem, or doripenem) for at least three days. Patients were excluded from the present study if they had been prescribed parenteral beta-lactam antibiotics in the two weeks prior to admission, had a documented adverse reaction to beta-lactams, or were not able to receive parenteral administration. Written informed consent was obtained from each subject before enrollment. Subjects were removed from the present study if they experienced any severe adverse events such as anaphylaxis, severe skin rash, severe hepatotoxicity, seizure, severe cytopenia, or severe antibiotic associated diarrhea. Baseline characteristics were recorded including age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) II score at enrollment, underlying disease, type of infection (community acquired, or hospital associated), and site of infection. Patients who required intravenous beta-lactam therapy were classified into PI and II according to the prescription of the attending physician. PI was defined as slow intravenous administration over a 3- to 4-hour period, whereas II was a conventional intravenous infusion completed within 15 to 30 minutes. Sepsis was defined by clinical and laboratory criteria according to the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference[16].

Outcomes

The primary outcome was 28-day survival. Secondary outcomes included clinical and microbiological responses after initiation of beta-lactam antibiotics. Favorable clinical outcomes comprised cure and improvement, while unfavorable outcomes comprised treatment failure, persistent infection, and new infection. Cure was defined as the disappearance of all signs and symptoms related to infection. Improvement was defined as a marked or moderate reduction in severity and/or signs and symptoms of infection. Treatment failure was a worsening of signs and symptoms related to infection and poor or no response to the primary antibiotics or persistent infection without clinical improvement. New infection was defined as an appearance of signs and symptoms of infection from new organism(s). Microbiological response was classified as eradication (culture became negative and/or remained negative upon subsequent cultures), persistence (causative organisms were still identified at the end of therapy), and new infection (detection of any new organisms during the beta-lactam therapy).

Sample size was calculated from the survival rate of 40%[8] in patients treated with beta-lactam antibiotics. The authors hypothesized that the PI of antibiotics should improve the survival rate by at least 20%, and a 5% type I error and 20% type II error were accepted. Therefore, a sample size of 192 patients was required in each group.

Statistical analysis

The Chi-square test or Fisher's exact test were used to compare categorical variables. Continuous variables were compared using Student's t-test or the Mann-Whitney U test. For all analyses, a 2-sided p-value smaller than 0.05 was considered statistically significant.

Results

Two hundred nineteen patients were recruited, and six patients were excluded due to incomplete data. The remaining 213 patients were categorized according to the attending physician's orders with 109 patients in the II group and 104 patients in the PI group. No significant difference in age, gender, or other baseline characteristics between the groups were identified (Table 1). Most patients had underlying diseases. The three most common co-morbidities were cancer (44.6%), hypertension (41.3%), and diabetes mellitus (24.4%). About 70% of infections from both groups were hospital acquired. Sepsis was significantly higher in PI group (p=0.02). Pneumonia, bacteremia, and urinary tract infection (UTI) were the major foci of sepsis in the present study. Bacteremia (p=0.03) and UTI (p=0.02) occurred significantly more often in the PI group than in the II group. Piperacillin/tazobactam (41.3%) followed by meropenem (36.6%) were the most frequently prescribed beta-lactam antibiotics. Patients in the II group mainly received piperacillin/tazobactam (49.5%) therapy while meropenem was

Table 1. Baseline characteristics of acutely ill patients with sepsis

Variables	II (n = 109) n (%)	PI (n = 104) n (%)	p-value
Age (year), Median (min, max)	66 (18, 102)	63 (18, 94)	0.49
Sex			0.25
Male	65 (59.6)	53 (50.9)	
Female	44 (40.4)	41 (49.1)	
APACHE II, Median (min, max)	18 (7, 37)	19 (7, 36)	0.20
Underlying disease	109 (100)	102 (98.1)	0.23
DM	30 (27.5)	22 (21.2)	0.35
HT	45 (41.3)	43 (41.3)	1.00
CAD	14 (12.8)	9 (8.7)	0.45
Cancer	49 (45.0)	46 (44.2)	1.00
CHF	8 (7.3)	8 (7.7)	1.00
Neurological disease	22 (20.2)	22 (21.2)	0.99
Liver disease	8 (7.3)	7 (6.7)	1.00
Renal disease	14 (12.8)	10 (9.6)	0.59
Chronic lung disease	10 (9.2)	8 (7.7)	0.88
HIV infection	4 (3.7)	2 (1.9)	0.68
Others[a]	47 (43.1)	42 (40.4)	0.79
Previous ABX	56 (51.3)	48 (46.1)	0.53
Type of infection			
CAI	29 (26.6)	32 (30.8)	0.31
HAI	80 (73.4)	72 (69.2)	0.50
Sepsis	10 (9.2)	21 (20.2)	0.02
Site of infection			
Pneumonia	37 (33.9)	40 (38.5)	0.49
UTI	14 (12.8)	27 (25.9)	0.02
IAI	13 (11.9)	11 (10.5)	0.83
CRBSI	3 (2.7)	5 (4.8)	0.70
SSTIs	5 (4.5)	5 (4.8)	1.00
Bacteremia	13 (11.9)	25 (24.0)	0.03
CNS infection	0 (0.0)	1 (0.9)	0.48
Others[b]	17 (15.5)	4 (3.9)	<0.01
Type of beta-lactams			<0.01
Piperacillin/tazobactam	54 (49.5)	34 (32.7)	0.01
Meropenem	26 (23.9)	51 (49.0)	<0.01
Imipenem	13 (11.9)	11 (10.6)	0.76
Ceftazidime	14 (12.8)	6 (5.8)	0.12
Cefipime	2 (1.8)	1 (1.0)	1.0
Doripenem	0 (0.0)	1 (1.0)	0.49

CAD=coronary artery disease; CAI=community acquired infection; CHF=congestive heart failure; CNS=central nervous system; CRBSI=catheter related bloodstream infection; DM=diabetes mellitus; HAI=hospital associated infection; HT=hypertension; IAI=intra-abdominal infection; II=intermittent infusion; PI=prolonged infusion; SSTIs=skin and soft tissue infections; UTI=urinary tract infection

[a] Such as alcoholism, autoimmune diseases, on immunosuppressive therapy, chronic corticosteroid use, hematologic diseases other than malignancy

[b] Clinical sepsis with negative blood culture and unknown infectious foci

prescribed more frequently in the PI group (49%) ($p<0.01$). The most frequently identified pathogen was extended spectrum beta-lactamase (ESBL) producing *Escherichia coli*, originating mainly from UTI. The

Table 2. Etiologic organisms

Organism	II (n = 109) n (%)	PI (n = 104) n (%)	p-value
Escherichia coli, ESBL+	26 (23.8)	33 (31.7)	0.20
Klebsiella pneumoniae, ESBL+	3 (2.8)	2 (1.9)	1.00
Pseudomonas aeruginosa	4 (3.7)	8 (7.7)	0.20
Acinetobacter baumannii	3 (2.8)	2 (1.9)	1.00
Other gram-negative bacteria	14 (12.8)	13 (12.5)	0.94
Unknown	59 (54.1)	46 (44.2)	0.15

ESBL+=positive for extended spectrum beta-lactamase producing tested by combined disc method; II=intermittent infusion; PI=prolonged infusion

Table 3. Primary and secondary outcomes between II and PI groups

Outcome	II (n = 109) n (%)	PI (n = 104) n (%)	p-value
28-day survival	95 (87.2)	83 (79.8)	0.27
Clinical outcome			0.11
Favorable	81 (74.3)	80 (76.9)	
Unfavorable	28 (25.7)	24 (23.1)	
Microbiological response			0.91
Eradication	38/61 (62.3)	48/76 (63.2)	
Persistence	11/61 (18)	20/76 (26.3)	
New infection	12/61 (19.7)	8/76 (10.5)	

II=intermittent infusion; PI=prolonged infusion

causative pathogen was not identifiable in 49.3% of the patients (Table 2).

The 28-day survival was 87.2% in the II group and 79.8% in the PI group (p=0.27) (Table 3). There were no statistical differences in clinical outcome or microbiological response. From Table 4, site of infection and type of organism were not associated with 28-day survival rate, but pneumonia and infections caused by *Acinetobacter baumannii* and other gram-negative bacteria were associated with unfavorable microbiological responses. In addition, infection caused by *A. baumannii* exhibited more significant unfavorable clinical outcomes (p=0.01).

Only 2.8% (II) and 2.9% (PI) of subjects developed minor adverse reactions such as gastrointestinal disturbance, minor skin rash, and phlebitis from antibiotics infusion. No serious adverse reactions were observed.

Discussion

Multidrug resistant gram-negative bacteria such as ESBL producing *E. coli* and *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *A. baumannii* were the major etiologic agents. Nearly half of subjects had received antibiotics before the culture was performed, which likely contributed to the low isolation rates the authors observed. The type of beta-lactam antibiotic therapy was significantly different between the groups. The choice of antibiotic was made by the attending physicians and there was no randomization. Severe sepsis, especially with bacteremia, was more common in the PI group, which may have led physicians to prescribe meropenem as a primary agent more often than other narrower spectrum beta-lactams.

Beta-lactam antibiotics exhibit time-dependent killing activity and their efficacies depend on T>MIC (ref). Theoretically, PI is the optimal method to maintain serum drug concentrations above the MIC. The authors' study showed no significant difference in 28-day survival, favorable clinical outcome or microbiological outcome in both groups. These findings are consistent with a meta-analysis published in 2009 that included 14 randomized controlled trials (RCTs) of critically ill patients with sepsis, pneumonia, or intra-abdominal infection[9]. A 2013 meta-analysis found that rates of recurrence and super infection were comparable between continuous and intermittent intravenous administration[17]. In contrast,

Table 4. Factors associated with primary and secondary outcomes

Factor	Total n (%)	28-day survival n (%)	p-value	Clinical outcome, n (%)		p-value	Microbiological response, n (%)			p-value
				Unfavorable	Favorable		Eradication	Persistence	New infection	
All case	213 (100)	35 (16.4)		52 (24.4)	161 (75.6)		20/137 (14.6)	31/137 (22.6)	86/137 (62.8)	
Infection										
Sepsis	31 (14.6)	4 (11.4)	0.57	5 (9.6)	26 (16.1)	0.25	18 (20.9)	6 (19.4)	4 (20.0)	0.98
Pneumonia	77 (36.2)	13 (37.1)	0.89	20 (38.5)	57 (35.4)	0.69	21 (24.4)	18 (58.1)	9 (45.0)	<0.01
UTI	41 (19.2)	7 (20.0)	0.90	8 (15.4)	33 (20.5)	0.42	26 (30.2)	6 (19.4)	4 (20.0)	0.39
IAI	24 (11.3)	3 (8.6)	0.77	5 (9.6)	19 (11.8)	0.67	12 (14.0)	3 (9.7)	2 (10.0)	0.93
SSTIs	10 (4.7)	0 (0.0)	0.37	1 (1.9)	9 (5.6)	0.46	4 (4.7)	0 (0.0)	0 (0.0)	0.61
Bacteremia	38 (17.8)	7 (20.0)	0.72	9 (17.3)	29 (18.0)	0.91	25 (29.1)	7 (22.6)	2 (10.0)	0.20
Organism										
E. coli, ESBL+	59 (27.7)	12 (34.3)	0.34	17 (32.7)	42 (26.1)	0.36	38 (44.2)	10 (32.3)	6 (30.0)	0.33
K. pneumoniae, ESBL+	5 (2.3)	2 (5.7)	0.19	2 (3.8)	3 (1.9)	0.60	1 (1.2)	1 (3.2)	2 (10.0)	0.09
P. aeruginosa	12 (5.6)	2 (5.7)	1.0	2 (3.8)	10 (6.2)	0.74	5 (5.8)	3 (9.7)	0 (0.0)	0.37
A. baumannii	5 (2.3)	1 (2.9)	1.0	4 (7.7)	1 (0.6)	0.01	0 (0.0)	2 (6.5)	2 (10.0)	0.01
Other gram-negative bacteria	27 (12.7)	3 (8.6)	0.58	3 (5.8)	24 (14.9)	0.09	18 (20.9)	1 (3.2)	2 (10.0)	0.04
Unknown	105 (49.3)	15 (42.9)	0.41	24 (46.2)	81 (50.3)	0.60	24 (27.9)	14 (45.2)	8 (40.0)	0.18

ESBL+=positive for extended spectrum beta-lactamase producing tested by combined disc method; IAI=intra-abdominal infection; II=intermittent infusion; PI=prolonged infusion; SSTIs=skin and soft tissue infections; UTI=urinary tract infection

two observational studies demonstrated that clinical cure and 14-day mortality in continuous or extended infusion groups were superior to intermittent bolus dosing[14,18]. Subjects enrolled in the present study differed in important ways from those included in prior studies. Subjects from RCTs included in the meta-analysis were more heterogeneous with respect to demographic data and APACHE II scores. In the authors' study APACHE II scores were higher than in previous trials reflecting an increased clinical severity. The etiologic organisms the authors identified tended to be more resistant to antibiotics (Table 2). Furthermore, the previous studies evaluated specific antibiotics to treat single organisms or a particular source of infection[7,14], but the authors assessed multiple beta-lactam antibiotics for the primary treatment of sepsis from various sources of infection. This is a pragmatic approach to managing sepsis patients as the responsible pathogen and locus of infection are often not known early in the course of illness.

The mortality rate of the PI group was 20.2% and the II group was 12.8%. Previous studies reported mortality rates ranging from 10% to 30% with continuous infusion and 13% to 36% using intermittent dosing; differences that did not reach statistical significance[19-21]. Different beta-lactam antibiotics provided comparable outcomes in the authors' study. This unexpected finding has several plausible explanations. First, the present study aimed to study the effect of initial beta-lactam antibiotic treatment according to the infusion method, but a number of subjects received additional antibiotics after microbiological results became available. This may have affected our results. Second, in 49.3% of our sepsis patients, the authors were not able to identify the causative organism, which the MIC data including all of culture-positive organisms were not available. If the MIC of the organisms remains within susceptible low levels, there may be no discernible difference on the clinical or microbiological outcomes between II and PI. PI can maintain longer T>MIC at the site of infection, and infusion may achieve a superior outcome, especially in resistant organisms[5,6,8]. Additional study of the effect of PI or II to eradicate drug resistant organisms is needed. Finally, confounding factors such as disease severity, co-morbidity, and other therapeutic interventions may modulate the effect of beta-lactam infusion methods and treatment outcomes.

The authors observed no significant differences between the groups with respect to adverse events. Similar to other studies, only minor adverse reactions such as diarrhea, mild hepatotoxicity, phlebitis, and skin rash were reported[22].

The present study had limitations. The sample size was smaller than the targeted subject size. This resulted

in lower power to detect a significant difference. The cohort study had confounding factors that made discerning a real effect of beta-lactam administration more difficult. There had more bacteremic patients in the PI group and this could affect physician decision to use PI strategy rather than II strategy. Chytra et al found that continuous administration of meropenem is an independent predictor of microbiological success of severe infections in ICU patients[23]. However, about 44% of II patients and 27% of PI patients did not complete microbiological evaluation following the treatments. This may have resulted in an underestimation of the microbiological outcome. The authors did not measure the effect of other antibiotics, duration of treatment, or beta-lactam concentration level, factors that probably influenced the treatment outcome. Finally, cost effectiveness is an important outcome that the authors did not consider. Although individual antibiotics and drug administrative costs of continuous infusion were lower than bolus dosing, all hospital costs were not statistically different[24]. Thus, a prospective RCT including cost effective analysis is needed.

Conclusion

The authors did not find statistically significant differences in survival rate, clinical response, safety or microbiological outcomes between PI or II of empirical beta-lactam antibiotics for the treatment of acutely ill patients with sepsis.

What is already known on this topic?

Beta-lactam antibiotics is the cornerstone for empirical treatment of patients with sepsis, but whether II or PI is more preferable is still unclear.

What this study adds?

The present study found no significant differences in survival rate, clinical response, safety, or microbiological outcomes between PI or II of empirical beta-lactam antibiotics for the treatment of acutely ill patients with sepsis.

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Conflicts of interest

The authors declare no conflict of interest.

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