Research Article

Continuous versus intermittent administration of piperacillin–tazobactam in intensive care unit patients with ventilator-associated pneumonia

Fanak Fahimi, Somayeh Ghafari[1], Hamidreza Jamaati, Shadi Baniasadi, Payam Tabarsi, Arvin Najafi, Arnavaz Akhzarmehr[1], Seyed Mohammad Reza Hashemian

Abstract

Background and Aims: Ventilator-associated pneumonia (VAP) is one of the most common Intensive Care Unit (ICU)-acquired infection. The aim of this study was to compare the clinical outcome of continuous and intermittent administration of piperacillin–tazobactam by serial measurements of the Clinical Pulmonary Infection Score (CPIS). **Subjects and Methods:** Groups were designed as parallel and the study was designed as quasi-experimental and conducted at a semi-closed ICU between September 2008 and May 2010. Patients received 3.375 g (piperacillin 3 g/tazobactam 0.375 g) either through intermittent infusion every 6 h for 30 min [Intermittent Infusion (II) group; *n* = 30] or through continuous infusion every 8 h for 4 h [Continuous Infusion (CI) group; *n* = 31]. CPIS was used to assess the clinical diagnosis and outcome of VAP patients. **Results:** Sex, age, Acute Physiology and Chronic Health Evaluation II II score on ICU admission, diagnosis and underlying disease of VAP patients were not significantly different in the CI (*n* = 31) and II (*n* = 30) groups. Duration of mechanical ventilation, length of stay, total number of antibiotics used per patient and duration of piperacillin/tazobactam treatment were similar in both groups. Mortality rates of VAP patients were similar between both groups during hospitalization. **Conclusion:** There was no significant difference in clinical outcomes of patients receiving piperacillin–tazobactam via CI or II when measured by serial CPIS score.

Key words: Piperacillin, tazobactam, ventilator-associated pneumonia

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.102083

Quick Response Code:

Introduction

Ventilator-associated pneumonia (VAP) is one of the most common Intensive Care Unit (ICU)-associated infections in patients who receive ventilation support, which would prolong ICU and/or hospital lengths of stay, and induce high mortality rate and heavy financial burden on health care services.[1] The patient outcome could considerably develop by early and precise diagnosis, more selective anti-microbial use and better routes of administration.[2,3] Piperacillin–tazobactam is a broad-spectrum β-lactam-β-lactamase inhibitor antibiotic used for the treatment of critically ill patients with VAP.[4] It is recognized that β-lactams are time-dependent antibiotics and that their effectiveness is in association with duration of free drug concentrations over the minimum inhibitory concentration (t > MIC) of organisms.[5] Although the routine mode of piperacillin administration is intermittent infusion (II), continuous infusion (CI) may also be advocated for improving the time above the MIC.[6] Animal studies have confirmed the greater efficacy of β-lactam CI over II.[5,7] However, the clinical benefit of CI or II of β-lactam antibiotics is in doubt in humans. Clinical outcomes such as mortality,[8-16] time to normalization of leukocytosis or pyrexia,[10,14,17,18] adverse events,[19] microbiological outcome,[18,20] duration of mechanical ventilation[11,15,17,20] and length of stay are comparable between bolus and

From:
Chronic Respiratory Disease Research Center, National Research Institute of Tuberculosis and Lung Disease, Masih Daneshvari Hospital, [1]Shahid Beheshti University of Medical Sciences, Tehran, Iran

Correspondence:
Dr. Seyed Mohammad Reza Hashemian, Chronic Respiratory Disease Research Center, National Research Institute of Tuberculosis and Lung Disease, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Daraabd st, Tehran, Iran. E-mail: smrhashemian@sbmu.ac.ir

continuous dosing of β-lactam antibiotics in seriously ill patients.[11,15,17,19] CI of β-lactam antibiotics may not also lead to a significant progression in the clinical cure compared with an intermittent bolus.[9-11,13,15,17,21,22] On the other hand, clinical cure[20,21] and 14-day mortality[23] of VAP patients could be significantly improved in the CI group compared with the intermittent bolus. Thus, further studies are required to evaluate the outcomes between continuous and intermittent administration of β-lactam antibiotics in critically ill patients. Here, in this study, we attempted to compare the clinical outcomes of continuous and intermittent administration of piperacillin–tazobactam by serial measurements of the Clinical Pulmonary Infection Score (CPIS).

Materials and Methods

Groups were designed as parallel and the study was conducted as quasi-experimental at the semi-closed Intensive Care Unit (ICU) in a university hospital between September 2008 and May 2010. All of the following criteria were necessary for diagnosis of VAP: white blood cell count >10,000 cells/mm^3 or <4000 cells/ mm^3; body temperature >38°C or <35.5°; new onset of purulent sputum or a change in sputum character; chest radiography indicating new or progressive infiltrate and a significant quantitative pathogen culture from respiratory secretions (tracheal aspirate >106 colony-forming units/mL or growth of ≥104 colony-forming units/mL of microorganism on bronchoscopic broncho alveolar lavage (BAL) culture) or isolation of the same microorganism in blood and respiratory secretions on Day 3 and Day 8. All of them should be older than 18 years, and the estimated length of ventilation is greater than 48 h. The presence of Gram-negative bacteria was verified by a significant quantitative culture from respiratory secretions Exclusion criteria were hypersensitivity or allergy to β-lactam antibiotics, pregnancy or lactation, neutropenia (<1000 cells/ mm^3), acquired immunedeficiency syndrome (AIDS), glomerular filtration rate (GFR) <60 mL/min by the Cockcroft–Gault equation, solid or hematological tumor and finding of any other known source of infection such as early-onset hospital-acquired pneumonia (HAP) or health-care-associated pneumonia (HCAP) without any risk factors for multidrug-resistant (MDR) pathogens according to the VAP guidelines.[4] Seventy patients were eligible to enter the study. Nine patients expired on Day 8 and did not complete the study protocol to the final analysis. Patients received 3.375 g (piperacillin 3 g/tazobactam 0.375 g) either by II every 6 h for 30 min (I) group; n = 30) or CI every 8 h for 4 h (CI group; n = 31). CPIS was used to assess the clinical diagnosis and outcome of VAP.[24] Also, Acute Physiology and Chronic Health Evaluation II (APACHE II) score was primarily used to predict the mortality of the patients.[25] Clinical and laboratory data conforming to the APACHE II score were recorded on admission and CPIS was measured at the onset of VAP symptoms (Day 1) and at Day 3 and Day 8. The definition for the day of onset of VAP was the day that the attending physicians made the clinical diagnosis (according to both prior inclusion criteria and based on CPIS >6) and prescribed antimicrobials for VAP. Demographic data, diagnosis at the time of admission, comorbidities, antibiotic regimen, duration of mechanical ventilation, length of stays and pathogen responsible for VAP were also recorded. The value of APACHE II was used in the prediction of mortality of VAP patients. For outcome criteria, mortality during hospital stay was applied. CPIS was monitored closely on Days 1, 3 and 8, and changes of each CPIS component were analyzed throughout the course of VAP therapy.

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA). Quantitative variables were reported as mean and standard deviation. Categorical variables were analyzed using the chi-square test or Fisher's exact test where appropriate, and continuous variable were compared using the Student T-test or Mann-Whitney U test. P-values <0.05 were considered significant.

Results

No significant differences were found between the CI (n = 31) and II (n = 30) groups for sex, age, APACHE II score on ICU admission, diagnosis and underlying disease of VAP patients. Mortality rates of VAP patients during hospitalization were similar in both groups. More deaths occurred in patients with a higher mean age (58.7 ± 19.9 years, P = 0.047). There were no significant differences in the duration of mechanical ventilation and length of stay between the two groups. The total number of antibiotics used per patient was similar in both groups. Duration of piperacillin/tazobactam treatment for VAP patients was not significantly different between the two groups [Table 1].

The distribution of bacterial pathogens isolated from BAL specimen on Days 1, 3 and 8 between the groups is displayed in Table 2. The most common microorganisms were Acinetobacter sp, *Pseudomonas aeruginosa, Klebsiella* sp, *Escherichia coli* and *Enterobacter* sp.

A time-dependent analysis of CPIS was conducted on the overall population and independently on patients who received CI or II of piperacillin/tazobactam. Our

Table 1: Baseline characteristics of patients with ventilator-associated pneumonia

Variables	CI (*n* = 31)	II (*n* = 30)	Total (*n* = 61)	*P* value
Age, years	49.41 ± 20.84	58.36 ± 22.11	53.81 ± 21.77	0.109
Gender, *n* (%)				
Male	16 (51.6%)	14 (46.7%)	30 (49.2%)	0.699
Female	15 (48.4%)	16 (53.3%)	31 (50.8%)	
APACHE II score on ICU admission	18.87 ± 5.95	20.43 ± 6.17	19.63 ± 6.06 (6–33)	0.319
Diagnosis, *n* (%)				
Cardiac and vascular disorders	10 (32.3)	9 (30)	19 (31.1)	0.849
Pulmonary disorders	17 (56.7)	18 (58.1)	35 (57.4)	0.912
Gastrointestinal disorders	2 (6.7)	5 (16.1)	7 (11.5)	0.425
Neurological disorders	3 (9.7)	2 (6.7)	5 (8.2)	>0.999
Infectious disease	5 (16.1)	5 (16.7)	10 (16.4)	>0.999
Neoplastic disorders	4 (12.9)	1 (3.3)	5 (8.2)	0.354
Trauma	2 (6.5)	2 (6.7)	4 (6.6)	>0.999
Sepsis	5 (16.1)	6 (20)	11 (18)	0.749
COPD	4 (12.9)	6 (20)	10 (16.4)	0.508
Post-CABG	4 (12.9)	0 (0)	4 (6.6)	0.113
Cystic fibrosis	2 (3.3)	0 (0)	2 (3.3)	0.492
Others	4 (6.6)	3 (4.9)	7 (11.5)	>0.999
Underlying diseases, *n* (%)				
Cardiac and vascular disorders	11 (18)	14 (23)	25 (41)	0.375
Pulmonary disorders	7 (11.5)	2 (3.3)	9 (14.8)	0.147
Gastrointestinal disorders	4 (12.9)	1 (3.3)	5 (8.2)	0.354
Neurological disorders	1 (3.2)	4 (13.3)	5 (8.2)	0.195
Infectious disease	4 (6.6)	0 (0)	4 (6.6)	0.113
Neoplastic disorders	3 (4.9)	1 (1.6)	4 (6.6)	0.612
Surgery	5 (8.2)	3 (4.9)	8 (13.1)	0.707
Trauma	3 (4.9)	2 (3.3)	5 (8.2)	>0.999
COPD	4 (13.3)	4 (12.9)	8 (13.1)	>0.999
CABG	4 (13.3)	3 (9.7)	7 (11.5)	0.707
Cystic fibrosis	2 (6.7)	2 (6.5)	4 (6.6)	>0.999
Others	0	5 (16.7)	5 (8.2)	0.124
Mortality rate, *n* (%)	17 (54.8%)	20 (66.7%)	37 (60.7%)	0.344
Duration of MV, days	42.61 ± 29.10	37.96 ± 28.23	40.32 ± 28.53 (9–118)	0.529
Length of ICU stay, days	39.9 ± 28.08	45.54 ± 31.39	42.77 ± 29.7 (9–128)	0.403
Length of hospital stay, days	43.76 ± 29.03	50.93 ± 32.79	47.40 ± 30.95 (12–136)	0.370
Number of drugs	22.8 ± 6.49	26.23 ± 6.61	24.49 ± 6.72	0.081
Number of antibiotics	5.09 ± 1.79	6 ± 1.92	5.54 ± 1.9	0.063
Number of antibiotics used in VAP	3.29 ± 1.07	4.1 ± 1.21	3.68 ± 1.2	0.548
Duration of piperacillin/tazobactam therapy, days	19.38 ± 10.5	18.16 ± 10.44	18.78 ± 10.41	0.651

MV = Mechanical ventilation; APACHE II = Acute Physiology and Chronic Health Evaluation; NOTE: Data are shown as mean ± SD or number (%) of patients, values in parentheses represent range. MV = Mechanical ventilation; APACHE II = Acute Physiology and Chronic Health Evaluation; COPD = Chronic obstructive pulmonary disease; CABG = Coronary artery bypass graft

Table 2: Pathogens responsible for VAP within the 8-day treatment

Pathogens	CI (*n* = 31)			IB (*n* = 30)			Total (*n* = 61)		
	Day 1	Day 3	Day 8	Day 1	Day 3	Day 8	Day 1	Day 3	Day 8
MDR-pathogens									
Acinetobacter sp	9 (29)	9 (29)	9 (29)	5 (16.7)	5 (16.7)	5 (16.7)	14 (23)	14 (23)	14 (23)
Pseudomonas aeruginosa	5 (16.1)	5 (16.1)	5 (16.1)	6 (20)	6 (20)	6 (20)	11 (18)	11 (18)	11 (18)
Enteric GNB									
Klebsiella sp	5 (16.1)	5 (16.1)	4 (12.9)	4 (13.3)	2 (6.7)	2 (6.7)	9 (14.8)	7 (11.5)	6 (9.8)
Escherichia coli	3 (9.7)	2 (6.5)	2 (6.5)	2 (6.7)	0	0	5 (8.2)	2 (3.3)	2 (3.3)
Enterobacter sp	2 (6.5)	2 (6.5)	1 (3.2)	2 (6.7)	2 (6.7)	2 (6.7)	4 (6.6)	4 (6.6)	3 (4.9)

MDR = Multiple drug resistance; GNB = Gram-negative bacilli; NOTE: Data are no. (%) of pathogens

results demonstrated that CI of piperacillin–tazobactam was not associated with a significant improvement in clinical outcomes when compared with II. The CPIS score declined from Day 1 to Day 3 (8.70 ± 2.13 vs. 7.04 ± 1.55); thereafter, CPIS illustrated tendency to incline again from Day 3 up to Day 8 (8.55 ± 2.13 vs. 8.70 ± 2.13) in the population as a whole [Figure 1]. The mean CPIS scores were similar in both groups on Day 1 (7.12 ± 1.33 vs. 6.96 ± 1.77; $P = 0.687$), Day 3 (8.74 ± 1.76 vs. 8.66 ± 2.48; $P = 0.892$) and Day 8 (8.51 ± 2.07 vs. 8.60 ± 2.22; $P = 0.880$). The CPIS components' scores were not significantly different between the two groups. Temperature did not show a

significant improvement during the 8-day treatment of VAP in both groups [Figure 2]. Leukocyte count declined until Day 3, and then inclined until Day 8 in both groups (12536.8 cells/mm^3 on Day 1, 13183.9 cells/mm^3 on Day 3 and 12041.9 cells/mm^3 on Day 8), but these changes were not significantly different in the two groups [Figure 3]. The PaO_2/FiO_2 ratio was not significantly increased in both groups. It increased from a value of 159.07 ± 79.9 on Day 1 to a value of 175.6 ± 67.3 on Day 3, and then decreased to a value of 162.7 ± 62.06 on Day 8. The PaO_2/FiO_2 increased from a value of 144.5 ± 64.9 on Day 1 to a value of 151.2 ± 57.6 on Day 3, and then decreased to a value of 142.5 ± 61.9 on Day 8 in the CI group [Figure 4]. Secretions did not show significant improvement within the 8-day treatment of VAP in both groups. The lung infiltrate did not show significant improvement within the 8-day treatment in both groups. The area under the curve (AUC) for receiver operating characteristics (ROC) curve was 0.543 (95% CI: 0.338–0.747) for CPIS on Day 1 in the CI group and 0.484 (95% CI: 0.273–0.695) for CPIS on Day 1 in the II group, 0.519 (95% CI: 0.316–0.721) for CPIS on Day 3 in the CI group and 0.534 (95% CI: 0.325–0.743) for CPIS on Day 3 in the II group, and 0.624 (95% CI: 0.435–0.813) for CPIS on Day 8 in the CI group and 0.602 (95% CI: 0.417–0.787) for CPIS on Day 8 in the II group; 0.578 (95% CI: 0.384–0.773) for APACHE II in the CI group and 0.614 (95% CI: 0.400–0.828) for APACHE II in the II group [Figures 5 and 6].

Discussion

Dosing for infections has been revised since developments of pharmacodynamic characteristics of antimicrobials and different patterns of their bactericidal activity.[26] Although the standard mode of administration of piperacillin is II, CI is of particular importance for optimizing the time above the MIC (t > MIC) in clinical cure improvement.[6] In addition, several studies have evaluated clinical outcomes including severity of illness,

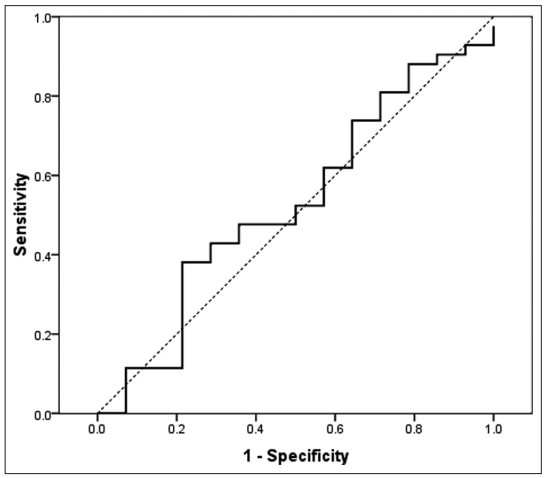

Figure 1: Clinical pulmonary infection score changes within the 8-day treatment in the studied groups

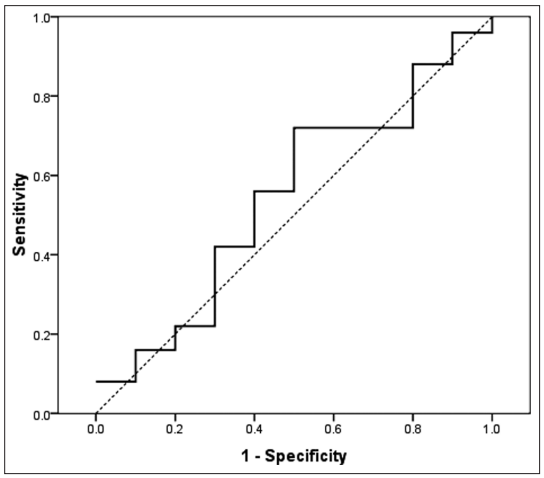

Figure 2: Temperature changes within the 8-day treatment in the studied groups

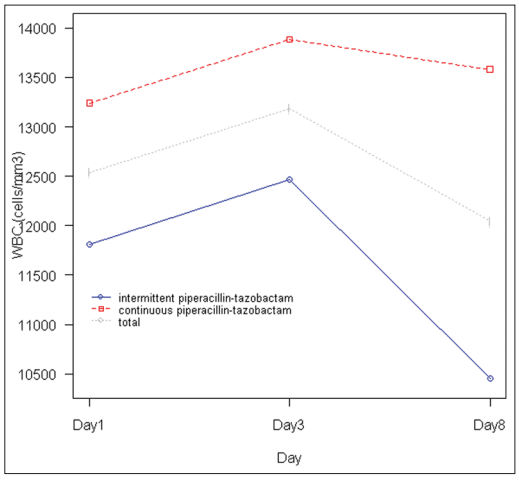

Figure 3: Leukocyte count changes within the 8-day treatment in the studied groups

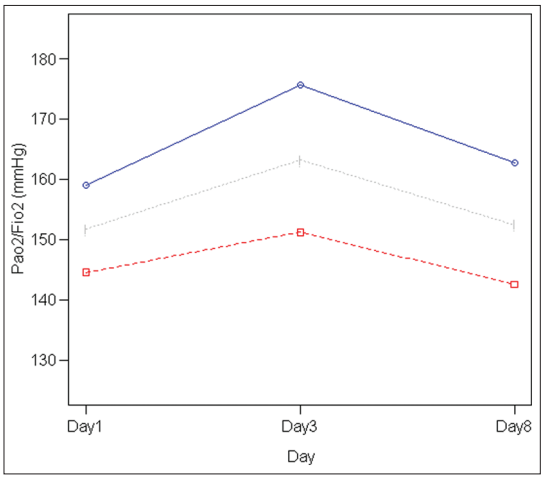

Figure 4: The PaO_2/FiO_2 ratio changes within the 8-day treatment in the studied groups

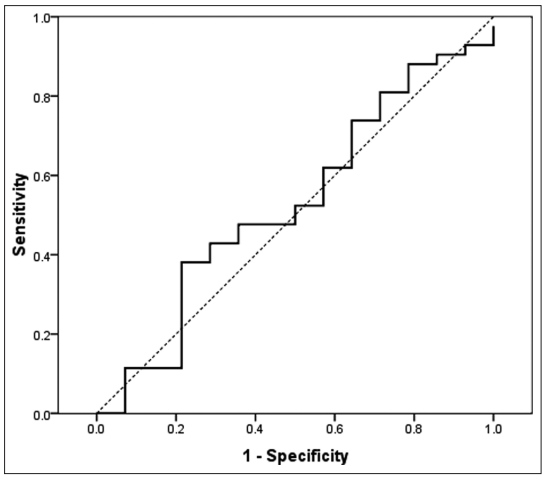

Figure 5: Receiver operating characteristic curve for acute physiology and chronic health evaluation II in the continuous infusion group

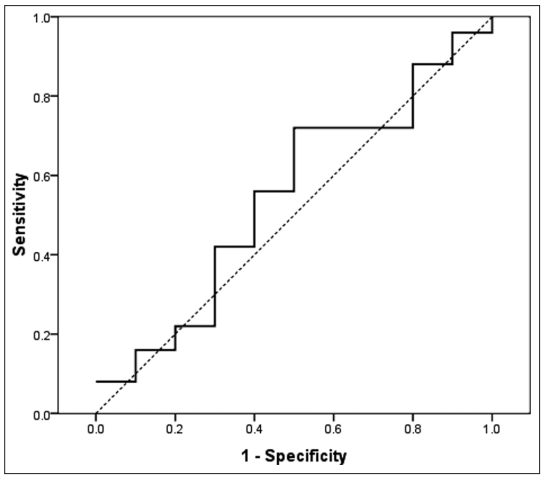

Figure 6: Receiver operating characteristic curve for acute physiology and chronic health evaluation II in the intermittent infusion group

duration of mechanical ventilation, mortality, clinical cure from actual infection, time to normalization of leukocytosis or pyrexia and lengths of ICU stay.[8-22] Similar to other studies,[11,20,23,27] no significant differences were found between the CI (n = 31) and the II (n = 30) groups in terms of sex, age, APACHE II score at ICU admission, diagnosis and microorganism responsible for VAP in this study. Consequently, mortality is not mainly dissimilar in the continuous and intermittent dosed groups.[8-11,13,14,20,27] Rapid improvement in PaO_2/FiO_2 has been granted as the most precise marker for adequate treatment. Duration of treatment was directly associated with the CPIS score at the time of pulmonary infection diagnosis in the Micek *et al*. study. [28] Also, duration of piperacillin–tazobactam therapy was correlated with the CPIS score at the onset of VAP symptoms (r = 0.364, P = 0.004), similar to our study. In this regard, CPIS scores from Day 1 to Day 8 and, more importantly, from Day 1 to Day 3 were not significantly different between the groups in our study. Although we observed that the temperature, leukocyte count (on Day 8), secretions and PaO_2/FiO_2 ratio (on Day 3) improved, these changes were mostly slight. We did not find any improvement in infiltrates. Similar studies have indicated limited value of chest radiography for clinical outcome assessment in patients with pneumonia,[29-31] while quickly deteriorating pathologies are indicative of either progression or recurrence of VAP. The PaO_2/FiO_2 ratio was the only parameter that increased slightly within 3 days of the onset, especially in group II, but did not achieve a normal value. Similar to our findings, Dennesen and coworkers demonstrated that temperature, PaO_2/FiO_2 ratio and leukocyte counts improved in time after initiation of antibiotic treatment, and the resolution of these parameters was generally slow.[32] Another study used CPIS to define whether a patient was responding to therapy, with most classic parameters of infection, such as amount and quality of secretions, radiographic infiltrate, leukocytosis and fever being poor indicators of t to therapy, while a more specific physiologic marker, the PaO_2/FiO_2 ratio, was more precise.[33] Temperature rise and leukocyte count are considered as reliable criteria for supporting VAP diagnosis; however, this may lead to incorrect decision because they are nonspecific markers in severely ill patients who suffer from sepsis, shock, physical stress or acute respiratory distress syndrome, or receive medications such as corticosteroids or b-agonists.[34,35] It emphasizes the effects of confounding factors such as underlying disease, prior antibiotic therapy, other medications in combination with piperacillin–tazobactam and previous treatment in each groups on outcome. In addition, lack of established criteria in our ICU compared with other studies produced a lower CPIS score on Day 3. Moreover, ample referral patients with preoccurred VAP episodes could have skewed our estimation for timing of VAP onset. Consequently, false and late diagnosis of VAP may have misleaded our CPIS scores on Days 1, 3 and 8. In previous VAP clinical trials, a wide range of mortality rates have been reported. By reviewing VAP studies since 1987, the rough mortality rates ranged from 24% to 76%. This wide range probably reflects differences in patient characteristics, underlying disease, diagnostic criteria and the pathogens involved.[36] According to another study, the mortality of Pseudomonas or Acinetobacter species-associated pneumonia was 87%, compared with a 55% mortality rate of pneumonia due to other organisms. [37] Similarly, Kollef *et al*. reported that patients with high-risk pathogens causing VAP (*Pseudomonas aeruginosa,* Acinetobacter spp and *Stenotrophomonas maltophilia*) had a considerably higher hospital mortality rate (65%) than VAP patients with other organisms (31%). [38] The mortality of 60.7% in the whole population, 66.7% in the II group and 54.8% in the CI group, of our study was close to those reports. *Pseudomonas aeruginosa* and Acinetobacter sp were detected as the most common

MDR pathogens in our study. In this study, the etiology of VAP isolated from the BAL specimen during the course of piperacillin–tazobactam therapy on Days 1, 3 and 8 did not significantly vary between the two groups. The predominant Gram-negative bacteria were Acinetobacter sp and *Pseudomonas aeruginosa*, followed by *Klebsiella* sp, *Escherichia coli* and *Enterobacter* sp. Several studies have reported that more than 60% of VAP is caused by aerobic Gram-negative bacteria.[39,40] The limitations of our study include the fact that the two modes of administration were not compared using a randomized design, piperacillin–tazobactam serum concentrations were not determined and the microbiological and laboratory data were not available as soon as other clinical information or at the favorite days. Also, it was performed within a single ICU and in a small sample.

Conclusion

In conclusion, there were no significant differences in the clinical outcomes of patients receiving piperacilin/tazobactam via CI or II by serial measurements of CPIS score. Therefore, we should emphasize that before choosing the standard mode of administering β-lactams, more randomized clinical trials are necessary to establish the potential advantage of administering β-lactams by CI or II in accordance with the MIC of the microorganism responsible, the ratio of tissue and serum concentration, the volume of distribution of the antimicrobial agent and the stability of the antimicrobial agent once dissolved between the two groups.

References

1. Joseph NM, Sistla S, Dutta TK, Badhe AS, Parija SC. Ventilator-associated pneumonia. Eur J Intern Med 2010;21:360-8.
2. Kollef MH, Schuster DP. Ventilator-associated pneumonia: Clinical considerations. AJR Am J Roentgenol 1994;163:1031-5.
3. Memish ZA, Cunningham G, Oni GA, Djazmati W. The incidence and risk factors of ventilator-associated pneumonia in a Riyadh hospital. Infect Control Hosp Epidemiol 2000;21:271-3.
4. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388-416.
5. Craig WA. Pharmacokinetic/pharmacodynamic parameters: Rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26:1-10; quiz 11-2.
6. Turnidge JD. The pharmacodynamics of beta-lactams. Clin Infect Dis 1998;27:10-22.
7. Vondracek TG. Beta-lactam antibiotics: Is continuous infusion the preferred method of administration? Ann Pharmacother 1995;29:415-24.
8. Angus BJ, Smith MD, Suputtamongkol Y, Mattie H, Walsh AL, Wuthiekanun V, *et al*. Pharmacokinetic-pharmacodynamic evaluation of ceftazidime continuous infusion vs intermittent bolus injection in septicaemic melioidosis. Br J Clin Pharmacol 2000;50:184-91.
9. Pédeboscq S, Dubau B, Frappier S, Hernandez V, Veyssières D, Winnock S, *et al*. [Comparison of 2 administration protocols (continuous or discontinuous) of a time-dependent antibiotic, Tazocin]. Pathol Biol (Paris) 2001;49:540-7.
10. Nicolau DP, McNabb J, Lacy MK, Quintiliani R, Nightingale CH. Continuous versus intermittent administration of ceftazidime in intensive care unit patients with nosocomial pneumonia. Int J Antimicrob Agents 2001;17:497-504.
11. Georges B, Conil JM, Cougot P, Decun JF, Archambaud M, Seguin T, *et al*. Cefepime in critically ill patients: Continuous infusion vs. an intermittent dosing regimen. Int J Clin Pharmacol Ther 2005;43:360-9.
12. Kojika M, Sato N, Hakozaki M, Suzuki Y, Takahasi G, Endo S, *et al*. [A preliminary study of the administration of carbapenem antibiotics in sepsis patients on the basis of the administration time]. Jpn J Antibiot 2005;58:452-7.
13. Lau WK, Mercer D, Itani KM, Nicolau DP, Kuti JL, Mansfield D, *et al*. Randomized, open-label, comparative study of piperacillin-tazobactam administered by continuous infusion versus intermittent infusion for treatment of hospitalized patients with complicated intra-abdominal infection. Antimicrob Agents Chemother 2006;50:3556-61.
14. Rafati MR, Rouini MR, Mojtahedzadeh M, Najafi A, Tavakoli H, Gholami K, *et al*. Clinical efficacy of continuous infusion of piperacillin compared with intermittent dosing in septic critically ill patients. Int J Antimicrob Agents 2006;28:122-7.
15. Roberts JA, Boots R, Rickard CM, Thomas P, Quinn J, Roberts DM, *et al*. Is continuous infusion ceftriaxone better than once-a-day dosing in intensive care? J Antimicrob Chemother 2007;59:285-91.
16. Sakka SG, Glauner AK, Bulitta JB, Kinzig-Schippers M, Pfister W, Drusano GL, *et al*. Population pharmacokinetics and pharmacodynamics of continuous versus short-term infusion of imipenem-cilastatin in critically ill patients in a randomized, controlled trial. Antimicrob Agents Chemother 2007;51:3304-10.
17. Hanes SD, Wood GC, Herring V, Croce MA, Fabian TC, Pritchard E, *et al*. Intermittent and continuous ceftazidime infusion for critically ill trauma patients. Am J Surg 2000;179:436-40.
18. Grant EM, Kuti JL, Nicolau DP, Nightingale C, Quintiliani R. Clinical efficacy and pharmacoeconomics of a continuous-infusion piperacillin-tazobactam program in a large community teaching hospital. Pharmacotherapy 2002;22:471-83.
19. McNabb JJ, Nightingale CH, Quintiliani R, Nicolau DP. Cost-effectiveness of ceftazidime by continuous infusion versus intermittent infusion for nosocomial pneumonia. Pharmacotherapy 2001;21:549-55.
20. Lorente L, Jiménez A, Martín MM, Iribarren JL, Jiménez JJ, Mora ML. Clinical cure of ventilator-associated pneumonia treated with piperacillin/tazobactam administered by continuous or intermittent infusion. Int J Antimicrob Agents 2009;33:464-8.
21. Buck C, Bertram N, Ackermann T, Sauerbruch T, Derendorf H, Paar WD. Pharmacokinetics of piperacillin-tazobactam: Intermittent dosing versus continuous infusion. Int J Antimicrob Agents 2005;25:62-7.
22. van Zanten AR, Oudijk M, Nohlmans-Paulssen MK, van der Meer YG, Girbes AR, Polderman KH. Continuous vs. intermittent cefotaxime administration in patients with chronic obstructive pulmonary disease and respiratory tract infections: Pharmacokinetics/pharmacodynamics, bacterial susceptibility and clinical efficacy. Br J Clin Pharmacol 2007;63:100-9.
23. Lodise TP Jr, Lomaestro B, Drusano GL. Piperacillin-tazobactam for Pseudomonas aeruginosa infection: Clinical implications of an extended-infusion dosing strategy. Clin Infect Dis 2007;44:357-63.
24. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. Am Rev Respir Dis 1991;143:1121-9.
25. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. Crit Care Med 1985;13:818-29.
26. Nicolau D, Quintiliani R, Nightingale CH. Once-daily aminoglycosides. Conn Med 1992;56:561-3. Erratum in: Conn Med 1992;56:694.
27. Patel GW, Patel N, Lat A, Trombley K, Enbawe S, Manor K, *et al*. Outcomes of extended infusion piperacillin/tazobactam for documented Gram-negative infections. Diagn Microbiol Infect Dis 2009;64:236-40.
28. Micek ST, Ward S, Fraser VJ, Kollef MH. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. Chest 2004;125:1791-9.
29. Fagon JY, Chastre J, Hance AJ, Guiguet M, Trouillet JL, Domart Y, *et al*. Detection of nosocomial lung infection in ventilated patients. Use of a protected specimen brush and quantitative culture techniques in

147 patients. Am Rev Respir Dis 1988;138:110-6.
30. Wunderink RG, Woldenberg LS, Zeiss J, Day CM, Ciemins J, Lacher DA. The radiologic diagnosis of autopsy-proven ventilator-associated pneumonia. Chest 1992;101:458-63.
31. Salata RA, Lederman MM, Shlaes DM, Jacobs MR, Eckstein E, Tweardy D, *et al*. Diagnosis of nosocomial pneumonia in intubated, intensive care unit patients. Am Rev Respir Dis 1987;135:426-32.
32. Dennesen PJ, van der Ven AJ, Kessels AG, Ramsay G, Bonten MJ. Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. Am J Respir Crit Care Med 2001;163:1371-5.
33. Luna CM, Blanzaco D, Niederman MS, Matarucco W, Baredes NC, Desmery P, *et al*. Resolution of ventilator-associated pneumonia: Prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. Crit Care Med 2003;31:676-82.
34. Garrard CS, A'Court CD. The diagnosis of pneumonia in the critically ill. Chest 1995;108 (2 Suppl):178-258.
35. Abramson N, Melton B. Leukocytosis: Basics of clinical assessment. Am Fam Physician 2000;62:2053-60.
36. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med 2002;165:867-903.
37. Fagon JY, Chastre J, Domart Y, Trouillet JL, Pierre J, Darne C, *et al*. Nosocomial pneumonia in patients receiving continuous mechanical ventilation. Prospective analysis of 52 episodes with use of a protected specimen brush and quantitative culture techniques. Am Rev Respir Dis 1989;139:877-84.
38. Kollef MH, Silver P, Murphy DM, Trovillion E. The effect of late-onset ventilator-associated pneumonia in determining patient mortality. Chest 1995;108:1655-62.
39. Torres A, Aznar R, Gatell JM, Jimenez P, Gonzalez J, Ferrer A, *et al*. Incidence, risk, and prognostic factors of nosocomial pneumonia in mechanically ventilated patients. Am Rev Respir Dis 1990;142:523-8.
40. Spencer R. Predominant pathogens found in the European prevalence of infection in intensive care study. Eur J Clin Microbiol Infect Dis 1996;15:281-5.

How to cite this article: Fahimi F, Ghafari S, Jamaati H, Baniasadi S, Tabarsi P, Najafi A, *et al*. Continuous versus intermittent administration of piperacillin-tazobactam in intensive care unit patients with ventilator-associated pneumonia. Indian J Crit Care Med 2012;16:141-7.

Source of Support: Nil, **Conflict of Interest:** None declared.