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

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

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 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

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. The patient outcome could considerably develop by early and precise diagnosis, more selective anti-microbial use and better routes of administration. Piperacillin–tazobactam is a broad-spectrum β-lactam-β-lactamase inhibitor antibiotic used for the treatment of critically ill patients with VAP. 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. 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. Animal studies have confirmed the greater efficacy of β-lactam CI over II. However, the clinical benefit of CI or II of β-lactam antibiotics is in doubt in humans. Clinical outcomes such as mortality, time to normalization of leukocytosis or pyrexia, adverse events, microbiological outcome, duration of mechanical ventilation and length of stay are comparable between bolus and
continuous dosing of β-lactam antibiotics in seriously ill patients. CI of β-lactam antibiotics may not also lead to a significant progression in the clinical cure compared with an intermittent bolus. On the other hand, clinical cure and 14-day mortality 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/mm³ or <4000 cells/mm³; body temperature >38°C or <35.5°C; 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/mm³), acquired immunodeficiency 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. 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. Also, Acute Physiology and Chronic Health Evaluation II (APACHE II) score was primarily used to predict the mortality of the patients. 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.
Table 1: Baseline characteristics of patients with ventilator-associated pneumonia

<table>
<thead>
<tr>
<th>Variables</th>
<th>CI (n = 31)</th>
<th>II (n = 30)</th>
<th>Total (n = 61)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>49.41 ± 20.84</td>
<td>58.36 ± 22.11</td>
<td>53.81 ± 21.77</td>
<td>0.109</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>16 (51.6%)</td>
<td>14 (46.7%)</td>
<td>30 (49.2%)</td>
<td>0.699</td>
</tr>
<tr>
<td>Male</td>
<td>15 (48.4%)</td>
<td>16 (53.3%)</td>
<td>31 (50.8%)</td>
<td></td>
</tr>
<tr>
<td>APACHE II score on ICU admission</td>
<td>18.87 ± 5.95</td>
<td>20.43 ± 6.17</td>
<td>19.63 ± 6.06 (6–33)</td>
<td>0.319</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac and vascular disorders</td>
<td>10 (32.3)</td>
<td>9 (30)</td>
<td>19 (31.1)</td>
<td>0.849</td>
</tr>
<tr>
<td>Pulmonary disorders</td>
<td>17 (56.7)</td>
<td>18 (60.0)</td>
<td>35 (57.4)</td>
<td>0.912</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>2 (6.7)</td>
<td>5 (16.7)</td>
<td>7 (11.5)</td>
<td>0.425</td>
</tr>
<tr>
<td>Neurological disorders</td>
<td>3 (9.7)</td>
<td>2 (6.7)</td>
<td>5 (8.2)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>5 (16.1)</td>
<td>5 (16.7)</td>
<td>10 (16.4)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Neoplastic disorders</td>
<td>4 (12.9)</td>
<td>1 (3.3)</td>
<td>5 (8.2)</td>
<td>0.354</td>
</tr>
<tr>
<td>Trauma</td>
<td>2 (6.5)</td>
<td>2 (6.7)</td>
<td>4 (6.6)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5 (16.1)</td>
<td>6 (20)</td>
<td>11 (18)</td>
<td>0.749</td>
</tr>
<tr>
<td>COPD</td>
<td>4 (12.9)</td>
<td>6 (20)</td>
<td>10 (16.4)</td>
<td>0.508</td>
</tr>
<tr>
<td>Post-CABG</td>
<td>4 (12.9)</td>
<td>0 (0)</td>
<td>4 (6.6)</td>
<td>0.113</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>2 (3.3)</td>
<td>0 (0)</td>
<td>2 (3.3)</td>
<td>0.492</td>
</tr>
<tr>
<td>Others</td>
<td>4 (6.6)</td>
<td>3 (4.9)</td>
<td>7 (11.5)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Underlying diseases, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac and vascular disorders</td>
<td>11 (18)</td>
<td>14 (23)</td>
<td>25 (41)</td>
<td>0.375</td>
</tr>
<tr>
<td>Pulmonary disorders</td>
<td>7 (11.5)</td>
<td>2 (3.3)</td>
<td>9 (14.8)</td>
<td>0.147</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>4 (12.9)</td>
<td>1 (3.3)</td>
<td>5 (8.2)</td>
<td>0.354</td>
</tr>
<tr>
<td>Neurological disorders</td>
<td>1 (3.2)</td>
<td>4 (13.3)</td>
<td>5 (8.2)</td>
<td>0.195</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>4 (6.6)</td>
<td>0 (0)</td>
<td>4 (6.6)</td>
<td>0.113</td>
</tr>
<tr>
<td>Neoplastic disorders</td>
<td>3 (4.9)</td>
<td>1 (3.3)</td>
<td>4 (6.6)</td>
<td>0.612</td>
</tr>
<tr>
<td>Surgery</td>
<td>5 (8.2)</td>
<td>3 (4.9)</td>
<td>8 (13.1)</td>
<td>0.707</td>
</tr>
<tr>
<td>Trauma</td>
<td>3 (4.9)</td>
<td>2 (3.3)</td>
<td>5 (8.2)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>COPD</td>
<td>4 (13.3)</td>
<td>4 (12.9)</td>
<td>8 (13.1)</td>
<td>&gt;0.999</td>
</tr>
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<td>CABG</td>
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<tr>
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<td>2 (6.7)</td>
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<td>&gt;0.999</td>
</tr>
<tr>
<td>Others</td>
<td>4 (6.6)</td>
<td>3 (4.9)</td>
<td>7 (11.5)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Mortality rate, n (%)</td>
<td>17 (54.8%)</td>
<td>20 (66.7%)</td>
<td>37 (60.7%)</td>
<td>0.344</td>
</tr>
<tr>
<td>Duration of MV, days</td>
<td>42.61 ± 29.10</td>
<td>37.96 ± 28.23</td>
<td>40.32 ± 28.53 (9–118)</td>
<td>0.529</td>
</tr>
<tr>
<td>Length of ICU stay, days</td>
<td>39.9 ± 28.08</td>
<td>45.54 ± 31.39</td>
<td>42.77 ± 29.7 (9–128)</td>
<td>0.403</td>
</tr>
<tr>
<td>Length of hospital stay, days</td>
<td>43.76 ± 29.03</td>
<td>50.93 ± 32.79</td>
<td>47.40 ± 30.95 (12–136)</td>
<td>0.370</td>
</tr>
<tr>
<td>Number of drugs</td>
<td>22.8 ± 6.49</td>
<td>26.23 ± 6.61</td>
<td>24.49 ± 6.72</td>
<td>0.081</td>
</tr>
<tr>
<td>Number of antibiotics</td>
<td>5.09 ± 1.79</td>
<td>6 ± 1.92</td>
<td>5.54 ± 1.9</td>
<td>0.063</td>
</tr>
<tr>
<td>Number of antibiotics used in VAP</td>
<td>3.29 ± 1.07</td>
<td>4.1 ± 1.21</td>
<td>3.68 ± 1.2</td>
<td>0.548</td>
</tr>
<tr>
<td>Duration of piperacillin/tazobactam therapy, days</td>
<td>19.38 ± 10.5</td>
<td>18.16 ± 10.44</td>
<td>18.78 ± 10.41</td>
<td>0.651</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>CI (n = 31)</th>
<th>IB (n = 30)</th>
<th>Total (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 3</td>
<td>Day 8</td>
</tr>
<tr>
<td>MDR-pathogens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acinetobacter sp</td>
<td>9 (29)</td>
<td>9 (29)</td>
<td>9 (29)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>5 (16.1)</td>
<td>5 (16.1)</td>
<td>5 (16.1)</td>
</tr>
<tr>
<td>Enteric GNB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klebsiella sp</td>
<td>5 (16.1)</td>
<td>5 (16.1)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>3 (9.7)</td>
<td>2 (6.5)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Enterobacter sp</td>
<td>2 (6.5)</td>
<td>2 (6.5)</td>
<td>1 (3.2)</td>
</tr>
</tbody>
</table>

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. 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. In addition, several studies have evaluated clinical outcomes including severity of illness,
duration of mechanical ventilation, mortality, clinical
cure from actual infection, time to normalization of
leukocytosis or pyrexia and lengths of ICU stay.\textsuperscript{[8-22]} Similar
to other studies,\textsuperscript{[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.\textsuperscript{[8-11,13,14,20,27]}
Rapid improvement in PaO\textsubscript{2}/FiO\textsubscript{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.\textsuperscript{[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\textsubscript{2}/FiO\textsubscript{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,\textsuperscript{[29-31]}
while quickly deteriorating pathologies are indicative of
either progression or recurrence of VAP. The PaO\textsubscript{2}/
FiO\textsubscript{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\textsubscript{2}/FiO\textsubscript{2} ratio and leukocyte counts improved in time
after initiation of antibiotic treatment, and the resolution
of these parameters was generally slow.\textsuperscript{[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\textsubscript{2}/FiO\textsubscript{2} ratio, was more precise.\textsuperscript{[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.\textsuperscript{[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 misled 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.\textsuperscript{[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.\textsuperscript{[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%).\textsuperscript{[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. 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 piperacillin/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


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