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New PK/PD profile improvement following cephalosporin extended infusion : a systematic review

Melisa Nurani[1], Widyati Widyati[2*], Nanang Yasin[3]

[1]*Departement of Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, 55281, Indonesia*
[2]*Faculty of Military Pharmacy, Indonesian Defense University, Bogor, 16180, Indonesia*
[3]*Departement of Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, 55281, Indonesia*

*Corresponding Author: E-mail: widyati@idu.ac.id

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ABSTRACT: Antimicrobial resistance is a global problem that is currently experienced in various countries, both developed and developing countries. The lack of discovery of new antibiotics and the increasing incidence of Multidrug–Resistant Organisms (MDROs) have sparked several efforts to optimize the administration of currently available antibiotics. Modifications in the pharmacokinetic and pharmacodynamic profiles are one of the strategies carried out, namely by extending the duration of infusion. Cephalosporins are time-dependent antibiotics; the longer they are exposed to an infusion, the more potent they are against bacteria. This is so that the drug concentration can remain above the MIC (Minimum Inhibitory Concentration) for an extended period of time throughout the infusion. In this study, articles available in Pubmed and Google Scholar from 2013-2023 using the PRISMA method related to the extension of the duration of cephalosporin infusion were evaluated. The search strategy used the keywords continuous infusion, extended infusion, prolong infusion, cefazolin, cefuroxime, ceftriaxone, ceftazidime, cefotaxime, and effectiveness. From the research results, it was found that continuous infusion was better able to achieve the desired target drug levels compared to intermittent infusion and IV bolus administration.

KEYWORDS: Cephalosporin; effectiveness; extended infusion; PK/PD profile.

INTRODUCTION

Infectious diseases, if not treated properly, will result in higher hospital care expenditures, mortality, and length of stay [1]. Early detection and administration of antibiotic therapy is the main standard for treating cases of infection [2]. Cephalosporins are β-lactam antibiotics which are classified into several generations based on their antibiotic activity, namely generations 1, 2, 3 and 4 [3].

Cephalosporin antibiotics have been widely used in health services because of their broad spectrum activity, affordable prices and easy to obtain supplies. Antibiotic overuse and misuse can lead to the development of resistant bacteria, which decreases the antibiotic's ability to kill germs [4]. The success of antibiotic therapy depends on the selection of appropriate empiric antibiotics, pharmacokinetic and pharmacodynamic (PK/PD) profiles, and the long duration of antibiotic administration [5]. One effort to increase the effectiveness of current antibiotic administration is by modifying the PK/PD profile.

The efficiency of cephalosporins as antibiotics in eradicating bacteria is time-dependent. Extending the time of infusion exposure can sustain the medication concentration above the MIC (*Minimum Inhibitory Concentration*) and achieve the maximal bactericidal level. The degree of bacterial killing is connected with the length of the infusion [5]. Recent research has demonstrated the advantages of prolonging the infusion period for time-dependent antibiotics, leading to a rise in antibiotic plasma concentrations of 4–8 times the minimum inhibitory concentration (MIC) and improved therapeutic results [6].

This systematic review attempts to explore the effect of extending the duration of cephalosporin antibiotic infusion on improving the PK/PD profile in patients who received both prophylactic and empirical antibiotics.

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MATERIALS AND METHODS

Data search strategy

A systematic literature review is what this study is. Finding data search methods or information sources from 2013-2023, choosing studies based on quality evaluation, synthesizing data, and extracting data are all steps in the research process. "continuous infusion" OR "extended infusion" OR "prolonged infusion" AND "cefazolin" OR "cefuroxime" OR "ceftriaxone" OR "ceftazidime" OR "cefotaxime" AND "effectiveness" were the keywords and boolean operators utilized in the literature search.

Information source

Google scholar, Sciencedirect, and Pubmed were the database sources utilized in this research to find literature.

Eligibility criteria

This study's eligibility requirements include both inclusion and exclusion standards. This study's inclusion criteria are:

a. Literature in the form of scientific journals,
b. Scientific journals sources come from Google Scholar and Pubmed,
c. Scientific journals have open access and can be accessed in full text,
d. Scientific journals use English or Indonesian,
e. Scientific journals publication year between 2013-2023 to show the latest research,
f. Discussions in scientific journals include the effect of extending the duration of cephalosporin infusion on improving antibacterial PK/PD profiles,
g. Scientific journals use prospective research designs,
h. Sample age ≥17 years in order to prevent an excessive number of dosage variations,

Exclusion criteria in this study:

a. Scientific journals use samples of pregnant and breastfeeding women to prevent variations in the profiles of pharmacokinetic and pharmacodynamic effects.

Researchers employed the PICO technique (Population/Problem, Intervention, Comparison, Outcomes) to restrict the study's scope, as shown in Table 1 below:

Table 1. PICO summary.

Component	Information
Population/Problem	Adult patients aged ≥17 years who received cephalosporin antibiotics either as prophylactic or empiric antibiotics
Intervension	Continuous or Extended or Prolonged Infusion of Cephalosporin
Comparison	IV Bolus or Intermittent Infusion of Cephalosporin
Outcomes	Achievement of target PK/PD profile of cephalosporin antibiotics

Quality assessment

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) method is used in the selection of literature. Figure 1 displays the PRISMA Flow Diagram used in this study. The PRISMA approach that was used yielded the following results: out of the 65 journal articles that were found, 21 were discarded due to data duplication, and the remaining 39 did not match the inclusion and exclusion criteria. Thus, the literature review uses five journal article because related and appropriate research is still infrequently conducted. CASP (Critical Appraisal Skill Program) is used in this study's quality assessment of the articles. There are twelve assessment components on the checklist for cohort studies and eleven assessment components for RCT studies. Five journals match the quality requirements and can be used as literature sources in this research, according to the assessment that was conducted.

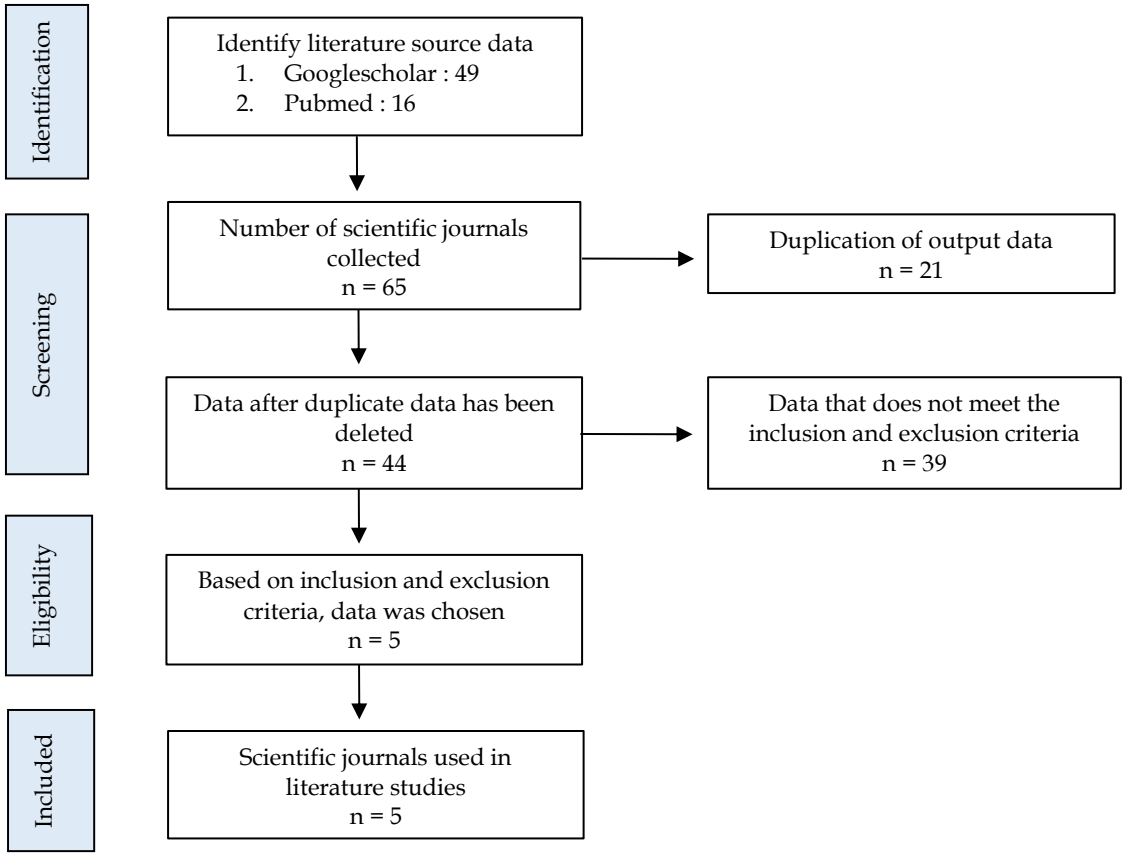

Figure 1. PRISMA flow diagrams.

Data synthesis

The literature that satisfied the inclusion and exclusion criteria, as well as the quality assessment, was compared as part of the data synthesis process in this study. Synthetic data pertains to the research goal, which is to evaluate the attainment of desired drug levels or PK/PD profiles for antibiotics belonging to the Cefalsporin class. These profiles were altered based on the length of infusion exposure, specifically comparing the effects of continuous infusion (infusion lasting 24 hours) versus intermittent infusion (infusion lasting 30 minutes) or IV bolus administration.

Data extraction

The identity of the investigator, the year of publication, the research design, the name of the antibiotic under evaluation, samples, and the findings from every study are all included in the data extraction output, which is presented as a table.

▪ RESULTS

All the main articles used to discuss the effectiveness of extending the duration of cephalosporin antibiotic infusion are summarized in Table 2.

Table 2. The effect of extending infusion cephalosporin.

Writer	Study design	Antibiotics	Sample	Results
Cousson et al.,2015	RCT	Ceftazidime	34 adult patients in ICU	Better pharmacodynamic outcomes are attained with continuous infusion of ceftazidime, which maintains consistent blood concentrations throughout treatment.
Naik et al.,2017	RCT	Cefazolin	20 patients who had major surgery	Target plasma concentrations can be reached with smaller infusion doses when cefazolin is administered continuously during intraoperative infusion.
Skhirtladze-Dworschak et al.,2019	RCT	Cefuroxime	12 adult patients undergoing elective cardiac surgery on CPB	Higher blood drug levels were achieved when Cefuroxime was given continuously as opposed to as part of an IV bolus.
Aardema et al.,2019	RCT	Cefotaxime	59 adult patients in ICU	Administration of Cefotaxime by continuous infusion achieves higher median drug levels compared to administration by intermittent infusion.
Leegwater et al.,2020	Prospective cohort	Ceftriaxone	55 adult patients in ICU	Continuous infusion of Ceftriaxone can lessen the chance that patients will be exposed to subtherapeutic dosages.

CABG : Coronary Artery Bypass Graft
CPB : Cardiopulmonary Bypass
ICU : Intensive Care Unit
RCT : Randomized Controlled Trial
VAP : Ventilator Associated Pneumonia

▪ DISCUSSION

In recent years, research has been carried out to prove the benefits of extending the duration of infusion when using time-dependent antibiotics, which in this case are cephalosporins. The PRISMA approach that was used yielded the following results: out of the 65 journal articles that were found, 21 were discarded due to data duplication, and the remaining 39 did not match the inclusion and exclusion criteria. Thus, the literature review uses 5 journal whose quality has been assessed using CASP (Critical Appraisal Skill Program). Synthetic data pertains to the research goal, which is to evaluate the attainment of desired drug levels or PK/PD profiles for antibiotics belonging to the Cefalsporin class. These profiles were altered based on the length of infusion exposure, specifically comparing the effects of continuous infusion (infusion lasting 24 hours) versus intermittent infusion (infusion lasting 30 minutes) or IV bolus administration.

A randomized controlled trial approach was used in a study by Cousson et al. (2015) on 34 adult ICU patients. There were two groups in the sample, each with seventeen patients. In patient samples with VAP caused by Gram-negative bacilli, one group received continuous infusion of ceftazidime (20 mg/kg body weight loading dose followed by a dose of 60 mg/kg/day); the other group received intermittent infusion (20 mg/kg body weight for 30 minutes every 8 hours). Ceftazidime levels in the epithelial lining fluid in BAL (Bronchoalveolar Lavage) rinses were measured for the study, with a target concentration of 20 mg/liter. The study's findings demonstrated that whereas intermittent infusion only attained the intended 46% of medication levels, continuous infusion achieved 100% of the target. Ceftazidime's average concentration in the epithelial lining fluid was 12 mg/liter in the continuous infusion group and only 6 mg/liter in the

intermittent infusion group. Furthermore, in the continuous infusion group, the threshold of 8 mg/liter in epithelial lining fluid was met twice as frequently as in the intermittent infusion group. Ceftazidime concentration in the epithelial lining fluid demonstrates that continuous infusion helps patients with VAP achieve their desired pharmacodynamic profile [7].

Naik et al. (2017) studied 20 adult patients who had extensive surgical procedures the following year, including multi-level spinal surgery and major urological surgery. By comparing the pharmacokinetic profiles of two distinct methods of administering the antibiotic Cefazolin perioperatively 10 individuals in group 1 receiving intermittent boluses at a dose of 2 grams every 4 hours, and 10 individuals in group 2 receiving continuous infusion the study employed an open label randomized controlled trial design. at a 500 mg dosage. The medication is administered until the skin closes again or the procedure is finished. They were each given two grams of cefazolin as a preventative antibiotic before to surgery. Blood samples are obtained from the patient both prior to and following the incision. The medication levels are then calculated, in this case by utilizing Monte Carlo Simulation to ascertain the fractional target attainment (FTA) and probability of target attainment (PTA). The findings of the study shown that superior FTA was obtained in >90% of S. aureus and E. coli isolates with continuous infusion of cefazolin with varying body weight and creatinine clearance during surgery. When compared to typical intermittent therapy (2 g every 4 hours), the PK/PD profile of cefazolin via continuous infusion demonstrated a noticeable improvement, even at modest dosages (500 and 1000 mg over 4 hours). More frequent repeat dose is necessary with intermittent dosing (every two or three hours) in order to obtain equivalent FTA to continuous infusion [8].

In 2019, Skhirtladze-Dworschak, et al. conducted an open label randomized controlled trial with 12 adult patients undergoing elective heart surgery on CPB, divided into 2 groups, to investigate different surgical prophylactic antibiotics. One group of six individuals received 1.5 grams of cefuroxime via IV bolus before to surgery; the dose was then repeated every 12 hours. Six other individuals received continuous infusion following 1.5 grams of cefuroxime via IV bolus, which was followed by a dose of 3 grams given over the course of 24 hours. The study's findings demonstrate that continuous infusion treatment leads in a greater Cmax 33 mg L-1 than IV bolus administration, which is 21 mg L-1. Additionally, continuous infusion administration produces a higher AUC 339 h mg L−1 than IV bolus therapy, which is 257 hmg L−1. Furthermore, a longer T>MIC % is obtained with continuous infusion as opposed to IV bolus delivery [9].

Aardema et al. carried out a second RCT study in 2020 on 59 adult ICU patients. The study compared the administration of Cefotaxime to two groups: one group, consisting of 30 individuals, received intermittent infusion (1 gram every 6 hours), while the other group, consisting of 29 individuals, received continuous infusion (4 grams/24 hours, following an initial dose of 1 gram for 40 minutes). This study's objective was to evaluate the total and unbound serum levels of Cefotaxime's active metabolites using LC-MS/MS, a proven analytical technique. Within one hour of the initiation of treatment, the target of at least 4 mg/L for total cefotaxime and at least 1 mg/L for unbound cefotaxime must be reached. The study's findings demonstrated that whereas only 50% of the Cefotaxime drug levels in the intermittent infusion group met the planned PK/PD target, 89.3% of the drug levels in the continuous infusion group did. In patients receiving continuous infusion, unbound cefotaxime concentrations were obtained and maintained at 96.4%, whereas in the intermittent infusion group, it was 71.4%. This study backs up the practice of giving the antibiotic Cefotaxime to patients in the intensive care unit for a longer period of time in order to maximize control over infection issues [10].

In 2020, Leegwater et al. carried out a prospective cohort research with 55 adult ICU patients who were split into two groups. For 30 minutes, Group 1's 30 participants received an intermittent infusion of Ceftriaxone at a dose of 2 grams every 24 hours. Group 2 comprised 25 individuals who were administered Ceftriaxone via continuous infusion at a dose of 2 grams over the course of 24 hours. An initial dose of 500 mg was administered to each group. Monte Carlo simulation was employed in the study to forecast the concentration of unbound Ceftriaxone after a 24-hour period. Samples of blood were drawn 10 and 22 hours following the start of treatment. A shortfall or excess dosage of Ceftriaxone may result from differences in clearance and volume of distribution experienced by critically ill individuals. The findings demonstrated that lower binding concentrations and, thus, lower PTA were linked to enhanced CLCR (creatinine clearance). Ceftriaxone administered intermittently results in >90% PTA (Probability of Target Attainment) in all simulations (ClCr 0–180 mL/minute), while continuous infusion results in >90% PTA only in patients with a reduction in ClCr (0–60 mL/minute). When compared to the intermittent dosing regimen of 2 g/12 hours or 2 g/24 hours, a greater percentage of patients reached a level of T>MIC 100% with continuous infusion at a

dose of 2 g/24 hours. According to this study, individuals with normal or enhanced clearance may experience subtherapeutic exposure while receiving intermittent doses of Ceftriaxone 2g/24 hours; however, continuous infusion can improve Ceftriaxone exposure [11].

The strength of this systematic review is that the included studies are prospective studies, particularly prospective cohorts and randomized controlled trials, so that the level of confidence in the research results is higher. The weakness is that the literature used is still limited and restricted to blood drug measurements. From the overall results of the study, it shows that the infusion extension method, namely continuous infusion on beta-lactam antibiotics, in this case cephalosporins, has a better PK PD profile compared to iv bolus or intermittent infusion. Stability of drug levels in the blood can improve the therapeutic outcome of treating patients with infections. This can be applied to deal with the incidence of antimicrobial resistance that is currently emerging in the world of health. We recommend using continuous infusion in treating infections in hospitals, especially in critically ill patients.

▪ CONCLUSION

Modifying the PK/PD profile, that is, increasing the length of infusion exposure to time-dependent antibiotics, in this example cephalosporins, can be used to sustain the effectiveness of currently accessible antibiotics. Due to the infusion's ability to sustain drug levels above the MIC, the longer the patient is exposed to the infusion, the greater the drug levels in the blood. Every study included in this evaluation produced results that were consistent with one another, meaning that continuous infusion produced higher levels than intermittent infusion or intravenous bolus. Still, the research is restricted to blood drug measurements. To evaluate the clinical results of patients who undergo intervention to prolong the duration of cephalosporin infusion, more research is required.

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