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THE EFFECTS OF PROLONGED INFUSION OF BETA-LACTAM ANTIBIOTICS ON SEPSIS: A LITERATURE REVIEW

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Abstract: Antibiotics are among the most used drugs in the context of critically ill patients, which is the case of septic patients, and the beta-lactam class is one of the most prescribed in these cases. In sepsis, there are protocols that must be followed, among them is the administration of broad-spectrum antimicrobials in the first three hours of diagnosis, as this measure is closely linked to the reduction of mortality in these patients. However, there are other factors that need to be taken into account and better analyzed in an attempt to also contribute to a positive outcome, such as the evaluation of the pharmacokinetics of these medications. Beta-lactams correlate their efficacy with time, that is, a better action is obtained when the serum concentration remains above the minimum inhibitory concentration of the pathogen for a longer period. In this perspective, the strategy of prolonged infusion of β-lactams has emerged as the standard treatment for sepsis or septic shock, despite its unknown efficacy. This study aimed to assess the efficacy of prolonged versus intermittent infusion of β-lactam antibiotics on outcomes in patients with sepsis or septic shock through a review using scientific databases. Prolonged infusion of β-lactam antibiotics significantly improved in achieving target plasma concentration and clinical cure without increasing the adverse event or the occurrence of antibiotic resistant bacteria. Prolonged infusion cannot improve hospital mortality, although an improvement has been demonstrated for studies published in or after 2015. More studies are needed, as suggested by a sequential analysis of trials.
Keywords: Beta-lactams, Antibiotics, Sepsis, Continuous Infusion.

INTRODUCTION

Antibiotics are among the most important drugs prescribed in the context of critically ill patients and beta-lactams, due to their broad spectrum of action, are one of the most used classes. However, over the years, bacteria have developed resistance to several classes of antibiotics, making it necessary to develop strategies to overcome this problem 2, 4.

In sepsis, a severe syndrome that is very common in medical practice, early initiation of broad-spectrum antimicrobials is protocol, more precisely within the first three hours of admission. This measure is essential in the support of septic patients because each hour of delay after the recommended time is associated with increased mortality and other negative outcomes. However, not only the correct choice of medication within the appropriate time interferes with the course of sepsis, but also the knowledge of the pharmacokinetics of the antibiotic.

The group of beta-lactam antibiotics can be used in cases of sepsis, therefore, as it is a serious condition, ways must be found to optimize your treatment. Knowing the pharmacokinetics of the drug and applying this knowledge in clinical practice can support a positive outcome. In this context, the strategy of prolonged infusion of β-lactams has emerged as the standard treatment for sepsis or septic shock, despite its unknown efficacy. This study aimed to assess the efficacy of prolonged versus intermittent infusion of β-lactam antibiotics on outcomes in patients with sepsis or septic shock through a review. In addition to explaining information about the time of administration of beta-lactam antibiotics in sepsis and identifying the benefits of prolonged infusion of beta-lactam antibiotics in sepsis in adult patients.

METHODOLOGY

The present study will be developed from a non-systematic literature review, in which several scientific articles that address the issue of prolonged infusion of beta-lactam antibiotics in the context of sepsis in adult

patients will be researched and analyzed.

The articles will be found through research in national and international scientific databases and those pertinent to the topic will be included in the form of a free literature review. Articles outside the topic will be excluded from this work.

The following terms were used as descriptors: infusion pumps, beta-lactams, antibiotics and sepsis. Finally, as a guiding question, the following sentence was used: What do scientific publications address regarding the effects of prolonged infusion of beta-lactams in the context of sepsis?

RESULTS

Critically ill patients with sepsis are prone to insufficiently low serum concentrations and consecutive treatment failure due to unique β-lactam PK changes. β-lactam PI evolved as a reaction to a better understanding of the PK/PD ratio of this group of antibiotics, whereby prolongation of fT > MIC/ECOFF subsequently leads to better antimicrobial exposure of the causative pathogens. Previous investigations have already suggested lower mortality rates and better clinical outcome using prolonged infusions in adults and pediatric patients. These effects are attributed to better target PK range during prolonged infusions. Critically ill patients included in the study by Roberts and Abdul-Aziz et al. they had median SOFA scores of only 6 (IQR 3-9) and had multiple sites of infection. Abdul-Aziz et al. demonstrated significantly lower mortality for β-lactam PI in patients with SOFA score ≥9 and in those with pneumonia. We analyzed a cohort of 414 patients critically ill patients with predominantly abdominal septic shock with a mean SOFA score of 13, predicting high a priori mortality. The monocentric nature of the study allowed for good comparability as described in the baseline characteristics provided. Unlike Rhodes et al, we exclusively evaluated only prolonged infusions of β-lactams. As a primary outcome measure, we found a significant reduction in mortality for the PI group. To control for interfering clinical properties, we performed a propensity score match and reanalyzed the primary outcome measure in the matched cohorts. Although the differences in mortality did not reach statistical significance, we still found markedly lower mortality rates when β-lactams were administered as PI. Due to the unequal number of patients in both groups, the generation of patient pairs as a prerequisite for matching was followed by a loss of about 50% of patients, making it unlikely that a chi-square test would reach the level of significance. Decreasing mortality rates by 10% in a cohort of patients with a high probability of death - statistically significant or not - is critically important to patients and clinicians. Kaplan-Meyer survival estimates show a divergence of survival curves, suggesting a significant impact ($p = 0.014$) of PI on the median survival probability. These findings strongly support the conclusion of a recently published review by Abdul-Aziz and colleagues that β-lactam PI may be especially important for critically ill/immunocompromised patients and those who are more likely to have less susceptible Gram-negative infections. To respond to the revised SSC guidelines, we amended our local sepsis protocol in 2017, which likely explains that patients in the PI group received TZB considerably more frequently (26%) between 2015-2017 (12%) while meropenem prescribing patterns has not changed. Major changes in the causative pathogens or an increase in infections caused by multidrug-resistant bacteria as a reason can be excluded. We also found a reduction in the duration of invasive ventilation for patients in the PI group. We would like

to argue that these effects are in line with prospective investigations that highlight the role of focus control and appropriate antibiotic treatment. On the other hand, uncontrolled or prolonged abdominal infection is accompanied by gastrointestinal paralysis with subsequent distention of the intestinal loops leading to a restrictive airway and a higher incidence of microaspiration. A discovery that is interesting from our study is that inflammatory markers such as C-reactive protein and procalcitonin showed similar courses. Although PI has been associated with lower mortality. One explanation is that CRP is an unreliable marker of infection in patients in surgical ICUs, as CRP levels can vary as a consequence of surgical trauma or liver failure. PCT is a primarily well-evaluated inflammatory marker for (lower) respiratory tract infections and a general marker for distinguishing bacterial from nonbacterial infections. Although PCT is routinely used in abdominal infections, its role in guiding therapy is still unclear. How the gut-lung axis and its role in immunomodulation contribute remains to be investigated. Unlike previous prospective studies, we included patients on RRT and/or hepatic dysfunction. TRS can have unpredictable effects on serum concentrations of hydrophilic β-lactams and PK target range, according to recently published work. We decided not to carry out a detailed assessment of the subgroup of patients receiving RRT for two reasons. First, serum concentrations were not available and the study did not focus on pharmacokinetic effects. Second, we intend to analyze the gross global effect of a representative cohort of patients with septic shock. With one fraction of 43% (IB) and 40% (PI), both cohorts show a very high fraction of patients in need of temporal RRT. The high rates of RRT stem from the inclusion criteria that focused on patients in septic shock. In addition, the baseline characteristics imply that the assessed cohort consists of elderly patients (IB: 65 years; PI: 66) with high VIS.

Despite reporting microbiological data, resistance data and MICs were not available. In addition, serum concentrations of β-lactams were not measured. Hitting PK targets is advised when treating critically ill patients. Unfortunately, our data does not allow linking the outcome (mortality) to specific PK targets. Until 2020, we have not implemented TDM-guided dose optimization in our department and adjusted β-lactam doses according to the manufacturers recommendation. Therefore, we were not able to investigate the toxicity of β-lactams nor could we link serum concentrations to the result. In this context, we expect the results of two interesting studies: The German TARGET study by Hagel et al. (DRKS00011159) investigates the impact of TDM-guided dose adjustments in the ICU on the survival of patients with sepsis and septic shock, while the Australian study BLING 3 (NCT03213990) is still recruiting patients to assess the effects clinical trials of continuously infused β-lactams versus intermittent bolus application.

DISCUSSION

We summarize the current evidence for an intravenous infusion strategy of β-lactam antibiotics in patients with sepsis or septic shock. Our study demonstrated that prolonged infusion significantly improved compared to intermittent infusion when target plasma concentration and clinical cure were achieved. In addition, the adverse event and the occurrence of antibiotic-resistant bacteria did not increase in the prolonged infusion group. Hospital mortality, however, did not differ significantly between groups.

β-lactam antibiotics are time-dependent drugs and their antibacterial activity is related to the duration of maintenance of their

concentration level above the MIC. Patients who received β-lactams by continuous infusion were ten times more likely to exceed the target MIC than patients who received intermittent infusion. Thus, our results can show a high clinical cure due to the high range of target plasma concentration. Based on the pharmacokinetic/pharmacodynamic principle and our results, clinicians must consider the prolonged infusion strategy of β-lactam antibiotics in the treatment of sepsis or septic shock.

In 2019, a systematic review was carried out, but the results were insufficient and failed to differentiate between continuous infusion and traditional intermittent infusions of antibiotics. However, the target population of a recent systematic review on an infectious disease (not sepsis) showed high heterogeneity for the included studies. However, our meta-analysis indicated low heterogeneity for the included studies, resulting in the inability of prolonged β-lactams to show superiority of results. Another previous systematic review showed improvement in hospital mortality with prolonged infusion of β-lactam antibiotics. This previous systematic study only examined antipseudomonal β-lactams, and some sensitivity analysis results could not show differences in mortality, which correlated with the results of our subgroup analysis. In addition, the study did not take into account adverse events or resistant strains.

Our current non-systematic review examined adverse events and the occurrence of antibiotic-resistant bacteria. Intermittent infusion resulted in a high number of adverse events due to the high peak concentration in intermittent infusion. However, no difference was observed, and this may be because β-lactams are generally considered to have a high safety window, even when high doses are used. Regarding the occurrence of antibiotic-resistant bacteria, there are very few data describing the prevention of bacterial resistance caused by prolonged infusion. Theoretically, the bacterial occurrence of antibiotic-resistant bacteria must not increase due to prolonged infusion, as a high clinical cure was demonstrated in the prolonged infusion group. Our results therefore support the claim that the prolonged infusion strategy can be safely performed without adverse events or an increase in antibiotic-resistant bacteria.

However, caution is required in our review process. We defined continuous and prolonged infusion as "prolonged infusion" to avoid possible eligible studies. In vitro evidence has demonstrated periods of time when free drug concentration exceeds the MIC for prolonged and continuous infusions. Several previous studies have also used "prolonged infusion" in research settings.

Our review has several limitations. First, the results may not apply to older patients, as the average age of enrolled patients was relatively young. For older patients, renal function may have deteriorated, resulting in a change in plasma concentration ofantibiotics. Second, there were only a few RCTs included in our analysis for several secondary outcomes: achievement of target plasma concentration, adverse events, and occurrence of antibiotic-resistant bacteria. More RCTs are needed in the future to support the results of our meta-analysis. Third, participants and healthcare staff were aware of group assignments in some of the included RCTs, which could result in performance bias. Therefore, we lowered the certainty of the evidence in our results. In contrast, we defined the prolonged infusion time as more than 1 h to include all possible studies. Cut-off time may affect the results, although our study only included continuous infusion in the prolonged infusion group. Finally, subgroup analysis was performed

retrospectively according to the year of publication (before and after 2015). Results may change if the analysis is performed prospectively.

FINAL CONSIDERATIONS

Prolonged infusion of β-lactam antibiotics significantly improved as target plasma concentration and clinical cure were achieved without increasing the number of adverse events or the occurrence of antibiotic-resistant bacteria. We could not show an improvement in hospital mortality in the prolonged infusion, despite recent meta-analysis studies showing an improvement in in-hospital mortality in subgroup analysis. The present study strongly endorses existing evidence from prospective studies and meta-analyses that favor β-lactam PI in critically ill patients. PI was associated with a clinically relevant reduction in mortality in a critically ill subpopulation of ICU patients with septic shock and shorter duration of ventilation.

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