Official title:	Efficacy of Betalactam Antibiotics in Prolonged Infusion Compared to Intermittent in Pediatric Patients With Sepsis
NCT number:	03019965
Date:	January 20, 2020

Methods

Study design

This was a prospective, three-center, open label clinical trial of prolonged infusion versus intermittent infusion (II) of piperacillin/tazobactam, imipenem or meropenem in patients with sepsis from three Pediatric third-level care Hospitals: (1) Unidad Médica de Alta Especialidad, Hospital de Pediatría de Centro Médico Nacional Siglo XXI del Instituto Mexicano del Seguro Social, Cd. México (approved November 15, 2016); (2) Hospital Infantil de México “Federico Gómez”, Cd. México (approved March 22, 2017); and (3) Hospital General Regional de Alta Especialidad del Bajío, León, Gto (approved July 13, 2017). Institutional ethics approval was obtained at each participating site, an annual reapproval in January 20, 2020. Written informed consent to participate in the study was obtained from each participant prior to study enrolment. The study was registered with the National Institutes of Health (NIH) trial registry (NCT03019965). All patients who were admitted between December 1, 2016, and December 1, 2019, were screened.

Participants and randomisation

Patients were eligible for inclusion if they developed sepsis (defined according to criteria established in the International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics), age > one month or < 17 years old, candidates to receive piperacillin/tazobactam, imipenem or meropenem as treatment. Exclusion criteria were as follows: patients with a history of allergy to one or more of the proposed antibiotics, patients with chronic kidney disease or acute renal failure, patients with acute liver failure of any cause and patients in

palliative or supportive care only, morbid obesity, and received more than 48 hours of treatment with piperacillin/tazobactam, imipenem or meropenem before the inclusion. Prior to the start of the research project, the allocation sequence was generated by mode of administration, using a table of random numbers with an allocation ratio of 1:1, no restriction was made to the randomization scheme. They were indicated in sealed numbered envelopes as: continuous (CI)/extended infusion (EI) or intermittent infusion (II). Once the informed consent letter was signed, the Medical Coordinator of each Hospital Unit contacted the main researcher (YFP) to indicate consecutively the assignment in 2 intervention groups, such as: Group 1. II.- patients who received piperacillin/tazobactam, imipenem, or meropenem in regular intermittent infusion. Group 2. CI/EI.- patients who received piperacillin/tazobactam in continuous infusion, imipenem or meropenem in extended infusion

Intervention

Group 1 received the antibiotic in II of piperacillin/tazobactam 300mg/kg/day based on piperacillin, divided into 4 doses/day (diluted in 5% glucose solution at a concentration of 50mg/ml, to be administered in 30 minutes, infusion every 6 hours), without exceeding a maximum dose of 16 g/day; imipenem 80mg/kg/day, divided into 4 doses/day (diluted in 0.9% saline solution at a concentration of 7mg/ml, to be administered in 60 minutes infusion, every 6 hours), without exceeding a maximum dose of 4g/day; or meropenem 100mg/kg/day, divided into 3 doses (diluted in 0.9% saline solution at a concentration of 7mg/ml, to be administered in 60 minutes infusion, every 8 hours), without exceeding a maximum dose of 6g/day; and Group

2 received the antibiotic in CI: to piperacillin/tazobactam initial doses 75mg/kg in 30 minutes infusion, immediately thereafter continue 300mg/kg/day, diluted in 5% glucose solution, at a concentration of 50mg/ml, to be administered in 24 hours infusion every 24 hours; imipenem initial doses 20mg/kg/doses in 60 minutes infusion, immediately thereafter continue 80mg/kg/day, diluted in 0.9% saline solution, at a concentration of 7mg/ml, to be administered in 6 hours infusion every 6 hours; or meropenem initial doses 35mg/kg/doses in 60 minutes infusion, immediately thereafter continue 100mg/kg/day, diluted in 0.9% saline solution at a concentration of 7mg/ml, to be administered in 8 hours infusion every 8 hours. Nursing staff were trained in the preparation and administration of antibiotics by administration modality, as well as continuous supervision of the maneuver. The study antibiotic was administered until the treating phisician decided to cease the drug, or substituted with other antibiotics if clinically indicated or according to the culture and susceptibility result if prescribed empirically; discharge; or death.

Outcomes and measurements

The primary clinical outcome was clinical cure at 14 days after antibiotic cessation, it was evaluated clinical response at 72 hours and 7 days. Clinical outcome was rated as either resolution: disappearance of all signs and symptoms related to the infection or failure: insufficient lessening of the signs and symptoms of infection to qualify as improvement, including death or indeterminate (no evaluation possible, for any reason). Secondary endpoints included adverse events occurring during or after administration of the antibiotics proposed, was evaluated as: none or adverse event classified according to the intensity of the clinical manifestation (severity) as:

mild, moderate or severe (2) and for each antibiotic (3). The evaluation was carried out in each hospital unit by 2 researchers

Sample size

It was calculated taking into account a difference between both groups of 15% superiority of continuous or extended infusion, starting from 50% for the intermittent infusion group and 65% for the intervention group, considering a confidence level of 95%, statistical power of 80%, a sample size of 134 was calculated; an estimated loss of 20%, a minimum of 170 patients per group would be required.

Statistical Analysis

The analysis was performed by intention to treat including all randomized patients who received at least one dose of antibiotic, although they have not concluded in the mode of administration to which it was assigned, and per protocol analysis to evaluate only the patients who received the assigned maneuver during all your treatment. Descriptive statistics to evaluate the baseline characteristics of the patients: calculation of simple frequencies and percentages for the qualitative variables, and for the mean or median quantitative variables according to their distribution, bivariate analysis with Pearson's Chi-square, Fisher's exact test and U Mann's -Whitney. The efficacy of the maneuver was evaluated by calculating the absolute risk reduction and the number needed to treat; evaluation of the safety of the intervention with analysis of the frequency of adverse events by treatment group. Multivariate logistic regression analysis to identify predictive variables associated

with clinical cure, adjusted for the main confounding variables found in the bivariate analysis, with a value of $p \leq 0.15$ were considered to build the model.