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Original Article

The evaluation of safety and efficacy of colistin use in pediatric intensive care unit: Results from two reference hospitals and review of literature

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ABSTRACT

Colistin, an old cationic polypeptide antibiotic, have been reused due to rising incidence of infections caused by multi-drug resistant (MDR) Gram-negative microorganisms and the lack of new antibiotics. Therefore, we evaluated safety and efficacy of colistin in treatment of these infections. This study included 104 critically ill children with a median age of 55,9 months between January 2011 and January 2016. Nephrotoxicity occurred in 11 (10.5%) patients. Nephrotoxicity occurred between the third and seventh day of treatment in 63% of colistin induced nephrotoxicity episodes. The subgroup analysis between the patients who developed nephrotoxicity during colistin treatment and those that did not, showed no significant difference in terms of age, underlying disease, cause for PICU admission and type of infection required colistin treatment, P values were 0.615, 0.762, 0.621, 0.803, respectively. All patients were receiving a concomitant nephrotoxic agent (P = 0,355). The majority of the patients (52%) were having primary or secondary immune deficiency in treatment failure group and the most common cause of PICU admission was sepsis in treatment failure group, P values were 0.007 and 0.045, respectively. Mortality attributed to colistin failure and crude mortality were 14.4% and 29.8%, respectively. In conclusion, colistin may have a role in the treatment of infections caused by multidrug-resistant Gram-negative bacteria in critically ill children. However, the patients have to be followed for side effects throughout colistin treatment, not for only early stage. And the clinicians should be aware of increase in the rate of nephrotoxicity in patients those have been receiving a concomitant nephrotoxic agent.

1. Introduction

Antibiotic resistance among Gram-negative bacteria has progressively disseminated to different countries worldwide, presenting a serious public health concern. Carbapenems, beta-lactam antibiotics with the broadest spectrum to Gram-negative microorganisms, have been used as a last resort for resistant Gramnegative infections. However, the recent increase in carbapenem-resistant pathogens has led to carbapenem failures and possibly

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contributing to an increased morbidity and mortality. The rising incidence of multi-drug resistant (MDR) Gram-negative infections and carbapenem-resistant Gram-negative (CRGN) since 2000s in pediatric intensive care units (PICU) continues to challenge clinicians. The lack of new antibiotics to combat these infections have led to the revival of colistin; an old class of cationic, cyclic polypeptide antibiotics [1]. Colistin is an active agent against selected gram-negative bacteria, including *Acinetobacter* species, *Pseudomonas aeruginosa*, *Enterobacteriacea* species. Nevertheless, colistin has been reported to have serious side effects such as nephrotoxicity and neurotoxicity in children and adults. Safety and efficacy data related to colistin use in children who were admitted to PICU is limited [2–8]. Therefore, we have aimed to determine the efficacy and safety of colistin in the treatment of serious nosocomial infections in PICU patients. The primary outcome of this study was to determine the safety of colistin. The secondary outcome was to determine the efficacy of colistin in treatment of CRGN infections. Herein, we present the experience of two tertiary PICU on safety and efficacy of colistin in the treatment of CRGN infections in critically ill children in PICU.

2. Materials and methods

This retrospective study included the patients admitted two reference hospitals located in Aegean region of Turkey, and received colistin empirically or for culture documented nosocomial infections, for a period of January 2011 and January 2016. Neonates and the patients who received colistin treatment $\leq$6 doses or $\leq$48 h were excluded from the study. All available medical records of the patients were reviewed. These included demographic characteristics, medical history, comorbidity, pathogens isolated and antimicrobial susceptibility of isolated pathogens, co-administration of other nephrotoxic agents, duration of PICU stay before isolation of resistant microorganisms, presence of medical devices, such as central catheters, urinary catheters, and endotracheal or tracheostomy tubes, ventriculoperitoneal device were recorded. The type of infection site (bloodstream, ventilator-associated pneumonia [VAP], ventriculoperitoneal shunt infection, etc), colistin administration route, duration and side effects, outcomes of antimicrobial therapy and prognosis were also recorded. The levels of serum urea, creatinine, C-reactive protein (CRP), the counts of leucocyte and platelets, procalcitonin if available, were recorded. Nephrotoxicity, neurotoxicity (seizures, change in level of conscious, neuromuscular blockade) and hypersensitivity due to colistin parenteral administration were recorded.

2.1. Microbiologic testing

Presumptive identification of Gram-negative pathogens was made using VITEK MS (bioMérieux, France). This cutting edge technology uses Matrix assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS) technology which is a new technology for species identification based on the protein composition of microbial cells. The isolate was tested for antibiotic sensitivity on Muller Hinton agar by Kirby Bauer disc diffusion technique using standard methods. The susceptibilities of amikacin, ceftriaxone, ceftazidime, piperacillin-tazobactam, cefoperazone-sulbactam, imipenem, meropenem, colistin and tigecycline were determined according to (EUCAST) guidelines [9].

2.2. Definitions

We reviewed the medical records of the enrolled patients and collected the case information. A standard form was used to achieve the epidemiologic data including age, sex, underlying diseases (pulmonary disease, malignancy, cardiovascular disease, hematologic/solid organ transplantation, metabolic disease, genetic syndrome, prematurity, renal disease, liver disease), medication or intervention (presence of tracheal cannula, central venous catheter, presence of a Foley catheter, mechanical ventilation, immunosuppressive therapy and steroid, receipt of antibiotics). The culture specimens of biologic samples were ordered by attending physician in the presence of symptoms and signs. Diagnosis of infection was based on clinical features and isolation of bacteria from normally sterile site. Nosocomial infection and ventilator associated pneumonia (VAP) were defined according to the Center for Disease Control and Prevention (CDC) definitions [10] and diagnosis of sepsis was made according to International Pediatric Sepsis Consensus [11].

MDR Gram-negative bacterial pathogens were defined by resistance to at least 3 classes of antimicrobial agents which are known to be effective against the respective pathogens [12]. A course of parenteral administration longer than 48 h was defined as continuous colistin administration. Clinical response was defined as a complete recovery from clinical findings of the infection. Microbiological response was defined as according to culture clearance at the end of therapy. Treatment failure was defined as the colistin course that clinical response could not be achieved. Failure of colistin therapy was defined as persistence or/and worsening of signs and symptoms or continuity of positive culture or radiologic deterioration. Breakthrough infection was defined in colistin administered patients if an infection occurred with another Gram (−) microorganism at least 72 h after the initiation of colistin treatment. Colistin was administered intravenously 5 mg per kg in three/four-divided doses according to body weight and creatinine clearance and 3.75 mg per kg via intraventricular route. Safety of colistin was assessed from all courses. Crude mortality was defined if a patient died during the study period. Attributable mortality was defined if a patient had a culture confirmed infection and died due to colistin failure.

Nephrotoxicity was defined as a blood creatinine level below 1.2 mg/dL and as an increase of >50% of the baseline creatinine level compared with baseline or a decline in renal function [2,6]. Use of additional nephrotoxic agents were queried included amphotericin B, aminoglycosides, cyclosporine, acyclovir, ganciclovir, vancomycin, intravenous contrast and other chemotherapeutic agents. Renal function results (urea, creatinine) were followed during colistin therapy and the results of first, third, seventh, and if continued fourteenth day were recorded if they were available.

Neurotoxicity was defined in conditions including paresthesia, neuromuscular blockade, seizures, change in level of consciousness, etc. during treatment. Cases with neurotoxicity were evaluated by Pediatric Critical Care Specialist and Pediatric Neurology Specialist.

2.3. Ethics

This study had the permission of the Ethical Board of Izmir Katip Celebi University [ethical decision number:58/March 24, 2016].

3. Results

During the study period January 2011 and December 2015, 104 patients received colistin therapy for culture-confirmed CRGN [n:82 (78.8%)] or empirically [n:22 (%21.2)] due to high incidence of CRGN infections. Empiric colistin treatment was administered to the patients who did not response to broad spectrum antibiotics or

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