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ORIGINAL RESEARCH ARTICLE

Treatment of Ventilator-Associated Pneumonia Using Intravenous Colistin Alone or in Combination with Inhaled Colistin in Critically Ill Children

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Abstract

Objective The objective of this study was to compare the safety and efficacy of inhaled plus intravenous (IV) colistin with that of IV colistin alone in critically ill children with ventilator-associated pneumonia (VAP) due to colistin-only susceptible (COS) Gram-negative bacteria (GNB).

Study Design and Patients This retrospective cohort study included critically ill children aged 1 month to 18 years with culture-documented monomicrobial VAP due to COS GNB.

Results Fifty patients were included, and 32 patients received IV colistin alone, whereas 18 patients received inhaled plus IV colistin. No between-cohort differences were observed in clinical ($p = 0.49$) and microbiological outcomes ($p = 0.68$), or VAP-related mortality ($p = 0.99$). Although the bacterial eradication rates did not differ in either treatment group, the median time to bacterial eradication (TBE) was significantly shorter in the inhaled plus IV colistin group than in the IV colistin group. The additional use of inhaled colistin was the only independent factor associated with TBE, and it shortened the median TBE by 3 days. Only one patient in the IV colistin group developed reversible nephrotoxicity. Mild bronchoconstriction was observed in three patients at the time of administration of the first doses of inhaled colistin, which did not require discontinuation of treatment.

Conclusions The present study has demonstrated that the addition of inhaled colistin to IV colistin led to a shorter TBE in critically ill children with VAP due to COS GNB. However, it did not lead to a significant difference in the clinical and microbiological outcomes of VAP.

Key Points

Addition of inhaled colistin to intravenous (IV) colistin did not lead to a significant difference in the clinical and microbiological outcomes of ventilator-associated pneumonia due to colistin-only susceptible Gram-negative bacteria in critically ill children.

Inhaled colistin may be a beneficial adjunct to IV colistin by leading to shorter time to bacterial eradication.

Mild bronchoconstriction may be seen at the time of administration of the first doses of inhaled colistin, which does not require discontinuation of treatment.

1 Introduction

Ventilator-associated pneumonia (VAP) is a common and serious complication for patients in the intensive care unit (ICU). The incidence of VAP caused by multidrug-

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resistant (MDR) Gram-negative bacteria (GNB), frequently resistant to most available antimicrobial agents, has increased significantly in recent years [1, 2]. Although abandoned in the early 1980s because of its nephrotoxicity and neurotoxicity, colistin has been brought back to clinical use for the treatment of infections caused by MDR GNB because of a paucity of new effective antimicrobial agents [3].

Colistin is administered in its inactive prodrug form, colistimethate sodium. It has been used intravenously, especially in critical care settings, for the treatment of VAP [2, 3]. However, the efficacy of intravenous (IV) colistin for treatment of lung infections has been debated because of its poor penetration into the pulmonary parenchyma [4, 5]. Colistin concentrations have been found to be undetectable in the lung tissue of piglets [4] and bronchoalveolar lavage (BAL) fluid of critically ill adult patients [5] after IV administration. Colistin can also be delivered through inhalation, which might be an alternative option for treatment of patients with VAP because the drug achieves high concentration in the respiratory tract while avoiding systemic effects [4, 6–8]. In a recent pharmacokinetic study, colistin concentrations were found to be much higher (approximately 100- to 1000-fold) in the pulmonary epithelial lining fluid than those in plasma after aerosol delivery [8]. Most data on the use of inhaled colistin have been derived from studies in adults [9–15] and patients with cystic fibrosis [6, 16, 17], and the experience with inhaled colistin as an adjunctive therapy for VAP in critically ill children has been limited. Hence, we conducted a retrospective cohort study to compare the safety and efficacy of inhaled plus IV colistin with that of IV colistin alone in critically ill children with VAP due to colistin-only susceptible (COS) GNB.

2 Materials and Methods

2.1 Study Design and Patient Population

This retrospective study was conducted in the paediatric intensive care unit (PICU) of Gazi University Hospital, a tertiary-care hospital in Ankara, Turkey. The study was approved by the Gazi University Hospital Institutional Review Board. From September 2010 to January 2014, critically ill children aged 1 month to 18 years with culture-documented monomicrobial VAP caused by MDR GNB susceptible only to colistin were included in the study. Data were collected by reviewing the PICU records, Microbiology Laboratory database, and our hospital-acquired infection surveillance data that were recorded using a database by hospital infection control practitioners. Eligible patients received ≥72 h of IV colistin and at least six doses of inhaled colistin for the treatment of VAP. Newborns, patients with cystic fibrosis, culture-negative cases, and asymptomatic patients with colonization were excluded from the study.

2.2 Colistin Administration

During the study period, the same colistin (colistimethate sodium) product (Colimycin; Kocak Farma, Istanbul, Turkey) was used for both IV and inhaled administration. Each vial contained colistin 360 mg, equivalent to 4.5 million IU or colistin 150 mg base activity. Colistin was diluted in 2 mL of sterile saline 0.9 % resulting in a concentration of 75 mg colistin base activity/mL and administered intravenously at a dosage of 2.5–5 mg/kg per day divided into two to four equal doses [18]. The dosage of inhaled colistin was 75 mg every 12 h for patients aged >1 year [18] and 4 mg/kg/dose every 12 h for patients aged ≤1 year [19]. It was diluted in 3 mL of sterile saline 0.9 % and administered via a vibrating-mesh nebuliser (Aeroneb Pro, Aerogen, Galway, Ireland). The solutions were prepared just before administration. For patients with ventilator support, the inhaled colistin was delivered by means of the Draeger Evita 4 Ventilator (Drager Medizintechnik GmbH, Lübeck, Germany).

2.3 Data Collection

The following variables were recorded, including demographic (age, sex, weight) and clinical characteristics of patients: underlying diseases, the Paediatric Risk of Mortality (PRISM III) score, the duration of PICU stay (before and after initiation of colistin treatment), the duration of mechanical ventilation (MV) (before and after initiation of colistin treatment), other antimicrobials given concomitantly, information about colistin administration (route, dosage, duration, adverse events), types and antimicrobial susceptibilities of isolated microorganisms, results of blood cultures and baseline laboratory tests that were obtained before the initiation of colistin treatment (total blood count, acute phase reactants, serum creatinine, blood urea nitrogen). Further outcome data, including clinical and microbiological outcomes of VAP, VAP-related mortality, and other-cause mortality were also recorded in all patients.

2.3.1 Treatment Groups

A course of IV colistin treatment was defined as the administration of at least 72 h of IV colistin (IV colistin group), and a course of inhaled plus IV colistin treatment was defined as concurrent administration of at least 6 doses of inhaled colistin as an adjunctive to 72 h of IV colistin (inhaled plus IV colistin group) in the same patient.

2.3.2 VAP Diagnosis

Diagnosis of VAP was made during the daily visits of the paediatric intensivist and paediatric infectious diseases (PID) consultant in conjunction with the infection control team, comprising a PID specialist and an infection control nurse practitioner, according to the criteria of the Centers for Diseases Control and Prevention [20]. VAP was diagnosed if a patient on MV for more than 48 h developed fever (>38.4 °C) or hypothermia (<36.5 °C), leucocytosis (leukocyte count of $\geq$15,000/mm^3), or leucopoenia (leukocyte count of <4000/mm^3), purulent tracheobronchial secretions (secretions that contain $\geq$25 neutrophils and $\leq$10 squamous epithelial cells per low power field, $\times$100), and new or progressive pulmonary infiltrates on chest radiograph [20]. The microbiological diagnosis of VAP was established by positive endotracheal aspirate (ETA) cultures growing a single COS strain of GNB. Diagnostic quantitative culture threshold was $\geq 10^6$ colony-forming units/mL [21]. Patients with a positive ETA culture lower than the predefined threshold, and those who had no clinical and radiologic findings of VAP, were considered to have colonization and were excluded from the study.

2.3.3 Colistin-Only Susceptible Gram-Negative Bacteria

Isolates of MDR GNB were defined as COS when they demonstrated full susceptibility to colistin and no susceptibility to all of the following antibiotics: ceftriaxone, cefotaxime, piperacillin-tazobactam, ticarcillin-clavulanate, aztreonam, ceftazidime, cefepime, cefoperazone-sulbactam, imipenem, meropenem, ciprofloxacin, levofloxacin, trimethoprim-sulphamethoxazole, gentamicin and amikacin for *Pseudomonas aeruginosa*, and, in addition, ampicillin-sulbactam for *Acinetobacter baumannii* [22].

2.3.4 Microbiology Studies

Bacterial identification and antimicrobial susceptibility testing of GNB was performed by using the BD Phoenix automated microbiology system (Becton Dickinson Diagnostic Systems, Sparks, MD, USA) according to the manufacturer's instructions. The breakpoints for susceptibility were those recommended by the Clinical Laboratory Standards Institute. Isolated bacteria were considered susceptible to colistin if the minimum inhibitory concentration was $\leq$2 mg/L [23].

2.4 Outcomes

The primary outcomes of the study were clinical and microbiological outcomes of VAP. As secondary outcomes, we evaluated the development of adverse events during colistin treatment, VAP-related mortality and other-cause mortality.

2.4.1 Clinical and Microbiological Outcome

Data from all patients were reviewed by two PID specialists (M.P. and A.T.) to assess the effectiveness (based on clinical and microbiological outcomes) and adverse events of colistin treatment. Clinical outcome was classified as follows: (i) favourable clinical response: clinical cure or clinical improvement (complete or partial resolution, respectively, of presenting symptoms and signs of pneumonia without requirement of any additional antibiotics at the end of the colistin treatment); (ii) poor clinical response: clinical failure (persistence or progression of presenting symptoms and signs of pneumonia during colistin treatment or death due to pneumonia while receiving colistin treatment) or recurrence (development of new episode of VAP at least 72 h after the clinical recovery of a previous episode) [10, 24].

According to the local policies for infection control in our hospital, bacteriologic sampling was performed routinely for all patients with VAP due to MDR pathogens every 2–3 days from initiation to discontinuation of the antibiotic treatment. The purpose of this frequent culturing was to determine the duration of isolation. Microbiological outcome was classified as bacterial eradication (no growth of the causative microorganism in the final cultures), bacterial failure (persistence of the causative microorganism on follow-up cultures regardless of the clinical outcome of the infection), and recurrence (re-isolation of the same pathogen regardless of the clinical outcome of the infection) [10, 24]. Time to bacterial eradication (TBE) was the duration of colistin treatment until the day of bacterial eradication, defined as the day that cultures first became negative and remained negative in repeated samples.

2.4.2 Adverse Events and Mortality

Nephrotoxicity in patients with normal renal function was defined as a 50 % or greater increase in serum creatinine level from the baseline and/or elevation of serum creatinine values beyond the estimated normal range for the patient's age group at any time during the treatment [25, 26]. Nephrotoxicity was evaluated by recording all serum creatinine values, which were obtained at baseline before the initiation of colistin treatment, every 2–3 days during treatment, and at the end of the treatment, as part of routine patient care. Adverse effects related to inhaled colistin treatment, such as bronchoconstriction, cough, apnoea or chest tightness, and arterial hypoxemia were recorded.

The severity of the clinical condition was assessed according to the PRISM III score on the day of admission to the PICU. Patients who died due to persisting or worsening

Table 1 Comparison of baseline demographic, clinical and microbial characteristics of the study patients

Characteristics	IV colistin group ($n = 32$)	Inhaled plus IV colistin group ($n = 18$)	p value
Age, median months (range)	18 (3–192)	13.5 (5–192)	0.69
Sex, male/female	15/17	7/11	0.58
PRISM III score, mean ± SD	12 ± 6.8	13.5 ± 9.5	0.86
Underlying disease, *n* (%)			
Chronic neurological or neuromuscular diseases	9 (28.1)	6 (33)	0.699
Inherited metabolic disorders	11 (34)	5 (28)	0.631
Malignancy	6 (18.7)	3 (16.6)	0.854
Primary immune deficiency	2 (6.2)	2 (11.1)	0.543
Others (chronic liver disease, congenital heart disease, thromboembolic events)	4 (12.5)	2 (11.1)	0.884
Isolated microorganism, *n* (%)			
Acinetobacter baumannii	25 (78)	12 (66)	0.375
Pseudomonas aeruginosa	7 (22)	6 (34)	0.375
Concomitant antibiotic treatment, *n* (%)			
Carbapenems	17 (53)	13 (72)	0.186
Glycopeptides	21 (65.6)	12 (66.6)	0.940
Aminoglycosides	11 (34)	10 (55.5)	0.145
Cefoperazone/sulbactam	8 (25)	1 (5.5)	0.085
Piperacillin/tazobactam	4 (12.5)	4 (22)	0.368
Fluoroquinolones	2 (6)	3 (16.6)	0.238
Duration of PICU stay before the initiation of colistin, median days (range)	21 (7–89)	24 (12–46)	0.504
Duration of PICU stay after the initiation of colistin, median days (range)	26 (5–96)	29 (10–38)	0.800
Duration of MV before the initiation of colistin, median days (range)	19 (7–72)	20 (12–32)	0.847
Duration of MV after the initiation of colistin, median days (range)	22.5 (5–76)	19 (6–36)	0.156
Daily dose of IV colistin, mg/kg, median (range)	3.2 (2.6–5)	3.4 (2.8–5)	0.69
Duration of colistin treatment, median days (range)	16 (10–22)	14 (5–21)	0.29

IV intravenous, *MV* mechanical ventilation, *PICU* paediatric intensive care unit, *PRISM* paediatric risk of mortality, *SD* standard deviation

signs of pneumonia while receiving colistin treatment were classified as VAP-related mortality, while patients who died due to all other non-VAP-related causes were classified as other-cause mortality.

2.5 Statistical Analysis

Data were analysed by frequency and percentage (%) for qualitative variables, and mean ± standard deviation (SD), median, minimum, and maximum values for quantitative variables. The data did not follow a normal distribution; therefore, the IV colistin and inhaled plus IV colistin groups were compared using the Mann–Whitney *U* test, Pearson Chi-square test, Fisher's Exact test, and Fisher–Freeman–Halton test. A multivariate regression analysis was performed to assess the relationship between the TBE and other factors. Statistical analyses were performed using IBM-SPSS version 21.0 and the significance was set at $p < 0.05$.

3 Results

During the 40-month study period, the annual VAP rates in our PICU ranged between 15.7 and 21 per 1000 ventilator days. Sixty critically ill children developed monomicrobial VAP caused by COS GNB and were treated with IV colistin. Fifty patients met all the criteria for enrolment, and 32 patients received IV colistin alone, whereas 18 patients received inhaled plus IV colistin treatment. According to the culture and susceptibility testing results, the causative pathogens were *A. baumannii* ($n = 37$) and *P. aeruginosa* ($n = 13$), which exhibited resistance to all available antibiotics, except colistin. Baseline laboratory tests (total blood count, acute phase reactants, serum creatinine, and blood urea nitrogen) were not different in either treatment group (see supplemental table in the electronic supplementary material). Concomitant bacteraemia with *P. aeruginosa* was seen in two patients with primary immune deficiencies that were treated with IV colistin alone in the

Table 2 Outcomes, adverse events, and mortality of patients in both treatment groups[a]

Outcome	IV colistin group ($n = 32$)	Inhaled plus IV colistin group ($n = 18$)	p value
Clinical outcome			
Favourable clinical response	23 (72)	15 (83)	0.362
Clinical cure	13 (56.5)	7 (46.7)	0.904
Clinical improvement	10 (43.5)	8 (53.3)	0.350
Poor clinical response	9 (28)	3 (17)	0.362
Clinical failure	6 (66.7)	3 (100)	0.854
Recurrence	3 (33.3)	0	NA
Microbiological outcome			
Bacterial eradication	23 (72)	15 (83)	0.362
Bacterial failure	8 (25)	3 (17)	0.494
Recurrence	1 (3)	0	NA
Time to bacterial eradication, median days (range)	6 (4–10)	3 (3–4)	<0.001
Adverse events			
Nephrotoxicity	1 (3)	0	NA
Bronchoconstriction	0	3 (16)	NA
Neurotoxicity	0	0	NA
Mortality			
VAP-related mortality	6 (18.8)	3 (17)	0.99
Other-cause mortality	6 (18.8)	5 (27.7)	0.48

IV intravenous, *NA* statistical analysis not available, *VAP* ventilator-associated pneumonia

[a] Data are presented as number (%) of patients, unless otherwise stated

clinical failure subgroup. In this study, all patients concomitantly received other IV antibiotics (Table 1) that were in vitro ineffective against the isolated pathogen in all VAP episodes. Development of resistance to colistin was not observed in either treatment group. Addition of inhaled colistin to IV colistin had no appreciable effects on the median duration of MV ($p = 0.15$) and the duration of PICU stay ($p = 0.8$) (Table 1). The comparative baseline characteristics of patients in both treatment groups are summarized in Table 1.

As shown in Table 2, there were no significant differences in clinical ($p = 0.49$), and microbiological outcomes ($p = 0.68$), and bacterial eradication rates ($p = 0.36$) between the two treatment groups. According to the follow-up culture results, bacterial eradication was achieved at a median of 3 days (3–4 days) in the inhaled plus IV colistin group, but was achieved at a median of 6 days (4–10 days) ($p < 0.001$) in the IV colistin group. To investigate whether the additional use of inhaled colistin was an independent factor associated with TBE, a multivariate linear regression analysis was used, with adjustments for underlying disease, isolated microorganism, concomitant antibiotic treatment, duration of PICU stay, and duration of MV. Only the additional use of inhaled colistin was the independent factor associated with TBE ($\beta = 3.2$; 95 % CI 2.48–3.95, $p < 0.001$), and it shortened the median TBE by 3 days.

All patients had normal renal function at the beginning of the colistin treatment, and only one patient (3 %) in the IV colistin group developed nephrotoxicity on treatment day 8. This patient was a 16-year-old boy with the diagnosis of thromboembolic events, and received concomitant vancomycin and radiocontrast agent that was administered for computed tomography angiography on treatment day 7. The patient's serum creatinine increased from 0.3 to 1.7 mg/dL, and returned to normal within 2 days after discontinuation of colistin treatment without renal replacement therapy. Because the patient received other nephrotoxic agents with colistin, this condition was not considered to be directly associated with colistin treatment. No patient developed clinically apparent neurotoxicity in either treatment group. Most of the patients tolerated inhaled colistin treatment well, and none of the patients was premedicated with inhaled β2-agonists. Only three patients (one with acute lymphoblastic leukaemia, and two with chronic neurological diseases) treated with inhaled colistin experienced bronchoconstriction and desaturation at the time of administration of the first doses, which did not require discontinuation of colistin treatment, and was substantially alleviated with inhalation of a β2-agonist. Additionally, no significant differences were observed regarding VAP-related ($p = 0.99$) and other-cause mortality ($p = 0.48$) in either treatment group (Table 2).

4 Discussion

The emergence of MDR *A. baumannii* and *P. aeruginosa*, which are resistant to almost all classes of antibiotics, and the lack of new and effective antimicrobial agents, led to the reconsideration of colistin as a valuable therapeutic option [3]. Inhaled colistin as an adjunct to systemic therapy appears promising for the management of patients with VAP due to MDR GNB [27, 28]. Safety and efficacy data regarding inhaled colistin use in paediatric patients are sparse. Only a few small case series have used inhaled colistin as monotherapy [29] or adjunctive therapy in paediatric patients with VAP [19, 30, 31]. To the best of our knowledge, this is the largest and the first paediatric cohort to date that compares the safety and efficacy of inhaled plus IV colistin with that of IV colistin alone in critically ill children with VAP due to COS *A. baumannii* and *P. aeruginosa.*

In the present study, we found favourable clinical and microbiological outcomes for both treatment groups. However, we could not find any significant differences in the clinical and microbiological outcomes between the two treatment groups, which may be attributed to our small cohort. Only a few comparative studies in adults [9–11, 14, 15] assessed the efficacy of inhaled colistin as an adjunct to systemic antibiotic treatment on the outcome of VAP caused by GNB. Although two recent retrospective comparative studies [11, 15] demonstrated better clinical cure rates with adjunctive inhaled colistin, other two retrospective studies [9, 10] and one randomized controlled study [14] found no beneficial effect on the clinical outcome. These comparative studies also showed conflicting results regarding the efficacy of inhaled colistin on the microbiological outcome [9, 10, 14, 15]. As in other studies [9–11, 14, 15], the additional use of inhaled colistin did not have any significant effect on mortality rates.

This study demonstrated that the additional use of inhaled colistin led to a reduced length of TBE in critically ill children with VAP due to COS GNB. Kuo et al. [32] found that the early eradication of MDR *A. baumannii* from the respiratory tract by inhaled colistin decreased the need for expenditure on patient isolation. Increased exposure to infected or colonized patients in the neighbouring hospital environment has been found to be a significant risk factor for the acquisition of multidrug-resistant strains, and poses a great challenge for infection control [33]. Early eradication could also minimize the opportunity for a population of organisms to develop resistance [21]. Prospective studies are needed to determine whether there is a subsequent reduction in the development of resistance, infections and outbreaks associated with persistent and repeated isolation of pathogens, or a decrease in hospital costs via reducing the need for isolation, with the additional use of inhaled colistin in critically ill children.

In clinical practice, colistin is frequently used as combination therapy, though there is a scarcity of data on whether combination therapy is superior to monotherapy [34]. Limited in vitro and clinical studies suggest that a synergism exists between colistin and other antimicrobial agents such as carbapenems, aminoglycosides, antipseudomonal β-lactams, fluoroquinolones, rifampin and trimethoprim-sulfamethoxazole [34, 35]. In the present study, all of the critically ill patients concomitantly received other intravenous antibiotics with documented resistance due to severity of infection, which might have influenced the efficacy data that could not be attributed solely to colistin.

The main adverse effects of colistin treatment are nephrotoxicity and neurotoxicity, which led to the discontinuation of its parenteral use in the early 1980s [3]. In the present study, only one patient in the IV colistin group developed reversible nephrotoxicity. The incidence of nephrotoxicity associated with IV colistin usage were found to be relatively low (0–22 %) in the recent paediatric reports [36–39] as opposed to ~50 % in older studies [40]. Possible explanations for the reported differences regarding nephrotoxicity between the previous and recent reports might include differences in dosing and formulations of colistin (colistin sulphate used in older studies is more toxic than the currently used form of colistimethate sodium), varying definitions of nephrotoxicity, improvements in supportive care in PICUs, close monitoring of renal function, and avoiding the use of concomitant nephrotoxic drugs [3, 34]. In this study, the addition of inhaled colistin to IV colistin did not lead to any systemic adverse events, and our results were consistent with those of the meta-analysis conducted by Valachis et al. [27]. Treatment with inhaled colistin may further be complicated with bronchoconstriction, which can be prevented or lessened by the addition of a β2-agonist either before or during nebulization [3, 41].

This study has the following limitations. Firstly, this is single-centre, retrospective study with a relatively small number of patients, and thus, cannot allow generalization of clinical and microbiological outcomes and adverse events. Secondly, concomitant use of other antibiotics with colistin might have influenced the outcomes. Thirdly, evaluation of neurotoxic side effects was difficult in children on MV who received sedatives and neuromuscular blockade agents. Finally, we were unable to measure the colistin concentrations in the plasma or BAL. Therefore, we could not evaluate the relationship between the colistin concentrations and the clinical and microbiological outcomes or adverse events in either treatment group. Further prospective studies about the pharmacokinetic/pharmacodynamic properties of colistin are needed in critically ill children.

Despite these limitations, this is the first comparative paediatric study that gives important data on whether the addition of inhaled colistin to IV colistin provides any additional therapeutic benefit to critically ill children with VAP due to COS GNB.

5 Conclusions

The present study has demonstrated that the addition of inhaled colistin to IV colistin led to a shorter TBE in critically ill children with VAP due to COS GNB. However, it was not followed by significant differences in the clinical and microbiological outcomes of VAP. Randomized controlled trials are needed to examine the efficacy and safety of inhaled colistin as an adjunctive therapy in paediatric patients.

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