Efficacy and Safety of Intravenous Colistin in Very Low Birth Weight Preterm Infants

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Abstract

Background Given the severity and high mortality of multidrug-resistant Gram-negative bacilli (MDR-GNB) infections, the use of colistin will increase in patients with MDR-GNB infection.

Objective This study aims to assess the efficacy and safety of intravenous colistin in very low birth weight (VLBW; birth weight < 1500 g) preterm infants.

Methods We retrospectively analyzed the medical records of patients who received colistin between June 2016 and December 2017. The patients were assigned to two groups: the VLBW group and the non-VLBW group. Both groups were evaluated for response to treatment and adverse effects.

Results In total, 66 infants who received colistin therapy were included; of these, 28 infants were VLBW. All of our patients received standard colistin treatment of 5 mg/kg per day in three doses and the median duration of colistin treatment was 14 days. No significant differences were observed between the groups with respect to the efficacy of colistin (defined as showing microbiological clearance in control cultures and the absence of mortality during treatment) (89.3 vs 86.8%, $p > 0.99$). Serum magnesium and potassium levels were significantly lower in the VLBW group than in the non-VLBW group during colistin therapy (magnesium, 1.30 vs 1.70 mg/dL, $p < 0.001$; potassium, 3.6 vs 4.6 mEq/L, $p < 0.001$). Acute kidney injury was observed in four infants in the VLBW group and one in the non-VLBW group, without significant differences ($p = 0.15$).

Conclusions Colistin administration appears to be efficacious in VLBW infants; however, renal function tests and serum electrolytes should be monitored more closely in these infants during treatment.

Key Points

This study aimed to compare very low birth weight (VLBW) preterm infants (28 patients) and non-VLBW infants (38 patients) in terms of efficacy and safety of intravenous colistin.

While no significant differences were observed between the groups with respect to the efficacy of colistin (89.3 vs 86.8%), serum magnesium and potassium levels were significantly lower in the VLBW infants than in the non-VLBW infants during colistin therapy.

Although colistin is effective in VLBW infants, renal function tests and serum electrolytes should be monitored more closely in these infants during treatment.

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1 Introduction

Healthcare-associated infections (HCAI) are an important cause of mortality and morbidity in neonatal intensive care units (NICUs). The incidence of HCAI has been reported to be 7–24% in NICUs [1, 2]. In recent years, the infections caused by multidrug-resistant Gram-negative bacilli (MDR-GNB) have increased, and options in the antimicrobial agents available for treating these infections have become limited. *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* are the most common microorganisms that cause MDR-GNB infections [3].

This increase in the frequency of MDR-GNB infections without new antibacterials in development has led to the consideration of the role of colistin therapy. Given the severity and high mortality of MDR-GNB infections, the use of colistin has increased in patients with MDR-GNB infections [4]. In previous years, depending on the parenteral use of colistin, higher rates of adverse effects including nephrotoxicity and neurotoxicity were reported [5]. However, recent studies have shown a reduction in the rates of nephrotoxicity due to better monitoring of adverse effects in intensive care units, using less toxic colistimethate sodium, and avoiding simultaneous use of other nephrotoxic drugs [6]. Clinical data concerning the effectiveness and safety of intravenous colistin administration in neonates remain limited [6–9].

This study aimed to assess the efficacy and safety of intravenous colistin administration in the treatment of MDR-GNB infections in very low birth weight (VLBW) preterm infants compared with more mature infants.

2 Material and Methods

2.1 Study Design and Data Collection

This retrospective, single-center study was conducted at the neonatology clinic of Harran University School of Medicine (a level III neonatal intensive care unit) in Sanliurfa, Turkey, between June 2016 and December 2017. The study was approved by the local ethics committee. We included infants who were administered intravenous colistin for > 72 h due to MDR-GNB infections. The age of the infants included in the study ranged between 4 and 120 days. Patients with acute kidney injury (AKI) before treatment or congenital urinary-tract abnormalities were excluded. Patients were assigned to one of two groups: the VLBW group (infants with birth weight < 1500 g) and the non-VLBW group (infants with birth weight > 1500 g).

The medical records of the participants were retrieved from hospital files. We recorded demographic data (gestational age, sex, and birth weight); underlying disease; comorbidities; surgical and invasive procedures; duration of stay in NICU; ventilator care; information regarding the administration of colistin (route, dosage, and duration) or other antibacterials (prior or concomitant to colistin therapy); use of nephrotoxic antimicrobial agents and/or medications; and laboratory tests, including microbiological (blood, urine, cerebrospinal fluid [CSF] cultures, and antibacterial sensitivity), biochemical (renal and liver functions and serum electrolytes), and hematological studies (complete blood count, C-reactive protein [CRP]). Microbiological clearance and clinical outcomes such as morbidity and mortality were also evaluated. Serum creatinine, magnesium, and potassium levels, blood urea nitrogen (BUN), and urine output were collected for assessing the possible side effects of colistin before intravenous colistin treatment, and 4–7 days after treatment was started.

2.2 Definitions

AKI was defined in accordance with a modified Kidney Disease: Improving Global Outcomes definition (KDIGO) staging system that Jetton and Askenazi [10] proposed on the basis of change in serum creatinine (Table 1). Standard definitions for nosocomial infections and clinical sepsis were used according to the Center for Disease Control and Prevention [11]. Severe sepsis was defined as sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Multidrug resistance was considered as resistance to at least three different antibacterial groups against Gram-negative pathogens. Treatment effectiveness was evaluated based on the clinical and microbiological response. The clinical response was defined as the resolution of initial signs and symptoms, tolerance to oral feeding, and weight gain. The microbiological response was defined as the detection of no bacteria in control cultures (blood, CSF, and urine), which were taken at least 3 days after intravenous colistin treatment. The tests were repeated weekly

Table 1 Modified KDIGO definition of AKI used in the study

AKI stage	Definition
0	No significant change in creatinine
1	↑ SCr by 0.3 mg/dL within 48 h or ↑ in SCr by 150–200% from previous trough
2	↑ in SCr by 200–300% from previous trough
3	↑ in SCr ≥ 300% from previous trough or SCr ≥ 2.5 mg/dL or RRT

AKI acute kidney injury, KDIGO Kidney Disease: Improving Global Outcomes, RRT renal replacement therapy, SCr serum creatinine

until the treatment was completed. The incidence of the patients who showed microbiological clearance in control cultures and survived during treatment was evaluated as the outcome measure of the efficacy of colistin.

2.3 Route of Colistin Administration and Dosage

All infants received intravenous colistin treatment 5 mg/kg per day given in three divided doses as an infusion in 5 mL saline over at least 30 min. The colistin formulation comprised 150 mg of colistin base-equivalent colistimethate sodium (Colimycin; Kocak Farma, Istanbul, Turkey). One milligram of colistimethate sodium was equal to 30,000 IU. The infants who were identified as having MDR-GNB infection based on their culture results and an outbreak of bloodstream infections caused by MDR-*Klebsiella pneumoniae* were administered colistin.

2.4 Microbiologic Methods

The BD BACTEC™ FX40 blood culture system (Becton-Dickinson Diagnostics, Sparks, MD, USA) was used to isolate microorganisms from blood. Tracheal aspirates, urine, and CSF specimens were inoculated into routine culture media (5% defibrinated sheep blood agar, chocolate agar, and an eosin-methylene blue agar plate). The microorganisms were identified by biochemical tests and the Vitek® 2 Compact system (bioMérieux, Marcy l'Etoile, France). The antimicrobial susceptibility to colistin was tested with the validated disk diffusion method based on the Clinical and Laboratory Standards Institute guidelines.

2.5 Statistical Analysis

Data were analyzed using SPSS statistical software (version 17; Chicago, IL, USA). The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to examine the distribution of data. Student's *t* test was performed to compare continuous parametric variables, Mann–Whitney *U* test to compare continuous nonparametric variables, and Chi-square test or Fisher's exact test to analyze categorical variables. The variables that had normal distribution were expressed as mean $\pm$ standard deviation, nonparametric continuous variables were expressed as the median (interquartile range), and categorical variables were expressed as numbers (%). *P* value < 0.05 was considered as statistically significant.

3 Results

In total, 1260 infants were admitted to NICU during the study period, and 152 (12%) of them were diagnosed with neonatal sepsis; of these, 72 patients were administered

intravenous colistin, and 66 of these patients were included. Six patients were excluded because of AKI or congenital renal anomaly before colistin therapy. Culture-proven sepsis was detected in 57 infants; the remaining nine patients received colistin empirically during an outbreak. Of the 66 patients in the study, 28 (42.4%) were VLBW infants, and 38 (57.6%) were non-VLBW infants. The primary diseases of the patients were respiratory distress syndrome (36%); surgical diseases (29%) such as intestinal atresia, meningomyelocele, omphalocele, gastroschisis, esophageal atresia, hydrocephalus, Hirschsprung disease; transient tachypnea of the newborn (20%); necrotizing enterocolitis (8%); and other causes (7%).

Table 2 shows the demographic data, baseline characteristics, and patient outcomes. Mortality was observed in 18 of the 66 patients without significant differences between the two groups ($p = 0.84$). Favorable clinical and microbiological outcomes were observed in 58 of the 66 patients (87.9%) (seven died during colistin treatment, one of the deceased patients during treatment and one patient who died 30 days after the completion of colistin therapy did not show microbiological clearance); no significant differences were observed between the two groups with respect to these outcomes ($p > 0.99$). No significant differences were found for mortality due to *Klebsiella* spp. infection between the two groups ($p = 0.35$) (Table 2). All infants received colistin intravenously; only one patient with ventriculitis and a ventriculoperitoneal shunt received it intraventricularly. Microbiologic clearance was not observed in two patients (3%); of these patients, one died on the eighth day of treatment, and the other one died 30 days after the completion of colistin therapy. Microorganisms were isolated from the blood cultures of 45 (68%) infants, the urine cultures of 14 (21%), the CSF cultures of two (3%), and the tracheal aspirate culture of only one. The use of carbapenem as a concomitant antibiotic was statistically higher in the VLBW group than in the non-VLBW group ($p = 0.03$, Table 3). In the present study, 95% of the microorganisms were resistant to penicillin, 88% to aminoglycosides, 86% to fluoroquinolones, and 85% to carbapenem; all isolated microorganisms (100%) were sensitive to colistin and tigecycline.

The incidence of AKI was higher in the VLBW group than in the non-VLBW group (four and one patients, respectively); however, no significance difference was observed ($p = 0.15$). During colistin treatment, the serum magnesium and potassium levels were significantly lower ($p < 0.001$ and $p < 0.001$, respectively) and the need for additional magnesium and potassium supplementation was statistically higher ($p < 0.001$) in the VLBW group than in the non-VLBW group (Table 3). The serum magnesium levels were significantly lower during colistin therapy than during the start of treatment in both groups ($p < 0.001$). Regarding serum

Table 2 Demographic characteristics and outcomes of the patients

	VLBW group (<i>n</i> = 28)	Non-VLBW group (<i>n</i> = 38)	<i>p</i> value
Gestational age (weeks)	28.1 ± 1.9	36.9 ± 2.8	< 0.001
Birth weight (g)	1159 ± 248	2675 ± 607	< 0.001
Male gender	19 (67.9%)	24 (63.2%)	0.69
Cesarean section delivery	27 (96.4%)	33 (86.8%)	0.23
5th minute APGAR score	5.1 ± 0.6	6.9 ± 1.1	< 0.001
Surgical disease	4 (14.3)	14 (36.8)	0.04
Previous antibiotic exposure ^a			
Aminoglycoside	1 (3.6%)	5 (13.2%)	0.23
Third-generation cephalosporin	2 (7.1%)	3 (7.9%)	> 0.99
Carbapenem	17 (60.7%)	22 (57.9%)	0.81
Vancomycin	5 (17.9%)	12 (31.6%)	0.21
Amphotericin B	2 (7.1%)	3 (7.9%)	> 0.99
Age at onset of infection (days)	15 (1–116)	14 (1–106)	0.71
Day of colistin started (days)	16 (3–120)	17 (4–109)	0.95
Duration of colistin therapy (days)	14 (3–21)	14 (4–21)	0.28
Duration of hospitalization (days)	65 (14–150)	41 (14–174)	0.13
Microorganisms			
<i>Klebsiella pneumoniae</i>	17 (60.7%)	24 (63.2%)	0.84
<i>Escherichia coli</i>	3 (10.7%)	4 (10.5%)	> 0.99
<i>Acinetobacter baumannii</i>	3 (10.7%)	3 (7.9%)	0.69
<i>Sphingomonas paucimobilis</i>	0 (0%)	2 (5.3%)	0.50
<i>Pseudomonas aeruginosa</i>	0 (0%)	1 (2.6%)	> 0.99
Outcome			
Total mortality	8 (28.6%)	10 (27.3%)	0.84
Mortality during colistin therapy	3 (10.7%)	4 (10.5%)	0.98
Efficacy of colistin	25 (89.3%)	33 (86.8%)	> 0.99
Mortality due to <i>K. pneumoniae</i>	7 (25.0%)	6 (15.8%)	0.35

Data are presented as mean ± standard deviation, median (range) or number (%)

VLBW very low birth weight

^aWithin 1 week before onset of infection

potassium levels during colistin treatment, although there was a significant reduction in the VLBW group ($p < 0.001$), no significant difference was observed in the non-VLBW group ($p = 0.46$) (Table 4).

4 Discussion

In recent years, there has been an increase in the number of studies evaluating the safety and efficacy of colistin in infants, including preterm infants [6, 9, 12–15]. Favorable outcomes have ranged from 76 to 91% in infants who were administered parenteral colistin treatment [6, 9, 13–17]. Cagan et al. [6] reported that 65 neonates received colistin therapy, and microbiologic clearance was documented in all of these patients; however, 14 patients (21%) in their study died during treatment. Jajoo et al. [13] stated that the persistence of *Acinetobacter* spp. on repeat culture was

detected in one of the 21 patients receiving colistin therapy, and they found that the efficacy of treatment was 76%. Alan et al. [9] demonstrated that colistin treatment had a high rate of efficacy, up to 80% in preterm infants with nosocomial sepsis with *A. baumannii*. In our study, the clinical efficacy was 88%. This result was consistent with those from other trials in neonates. The overall mortality in neonates who have been administered colistin therapy has been reported to vary between 9 and 33% in recent studies [6, 9, 12–16]. Jasani et al. [14] found a mortality rate of 33.7% (21 out of 62); mortality was significantly higher in neonates with lower body weights in their study. In the present study, the overall mortality was 27% (18 out of 66), which was consistent with the recent studies on newborns without significant differences between the VLBW and non-VLBW group.

The dosage of intravenous colistin recommended by manufacturers in the US is 2.5–5 mg/kg per day, divided

Table 3 Clinical and laboratory characteristics of patients

	VLBW group (<i>n</i> = 28)	Non-VLBW group (<i>n</i> = 38)	<i>p</i> value
Positive blood culture	21 (75.0%)	24 (63.2%)	0.31
Positive urine culture	3 (10.7%)	11 (28.9%)	0.07
Invasive mechanical ventilation (> 2 days)	17 (60.7%)	10 (26.3%)	0.005
Total parenteral nutrition (> 5 days)	22 (78.6%)	20 (52.6%)	0.03
Central venous catheter (during infection)	19 (67.9%)	12 (31.6%)	0.004
CRP at onset of infection (mg/dL)	6.4 ± 7.4	7.1 ± 8.4	0.92
Thrombocytopenia at onset of infection (< 100 × 10 ³ /mm ³)	13 (46.4%)	10 (26.3%)	0.09
Day of microbiological clearance (days)	4.6 ± 1.1	4.4 ± 1.5	0.63
Rate of microbiological clearance	27 (96.4%)	37 (97.4%)	0.67
Concomitant medications			
Diuretics (> 3 doses)	1 (3.5%)	4 (10.5%)	0.38
Ibuprofen	4 (14.3%)	2 (5.2%)	0.38
Carbapenem	24 (85.7%)	26 (68.4%)	0.03
Aminoglycoside	2 (7.1%)	9 (23.7%)	0.07
Amphotericin B	3 (10.7%)	3 (7.9%)	0.49
During colistin therapy			
Mg (mg/dL) (before correcting)	1.30 ± 0.33	1.70 ± 0.28	<0.001
Need for additional Mg supplementation	22 (78.6%)	9 (23.7%)	<0.001
K (mEq/L) (before correcting)	3.67 ± 0.96	4.64 ± 0.72	<0.001
Need for additional K supplementation	15 (53.6%)	2 (5.3%)	<0.001
Calcium (mg/dL)	8.55 ± 1.37	9.30 ± 0.80	0.02
Creatinine (mg/dL)	0.54 ± 0.26	0.40 ± 0.14	0.001
BUN (mg/dL)	21.1 ± 18.0	13.0 ± 13.8	0.01
Acute kidney injury	4 (14.3%)	1 (2.6%)	0.15
AST (IU/L)	55.7 ± 69.7	39.1 ± 36.3	0.51
ALT (IU/L)	27.0 ± 35.8	22.6 ± 18.7	0.13

Data are presented as mean ± standard deviation or number (%)

ALT alanine aminotransferase, AST aspartate transaminase, BUN blood urea nitrogen, CRP C-reactive protein, K potassium, Mg magnesium, VLBW very low birth weight

into 2–4 equal doses. The neonatal dosages of intravenous colistin used in recent studies ranged from 2.5 mg/kg per day to 5 mg/kg per day or from 25,000 to 75,000 IU/kg per day in 2–3 divided doses. The duration of colistin treatment ranged from 9 to 18 days [6, 12–14, 18]. In the present study, all infants were administered the standard 5 mg/kg per day in three doses, and the median duration of colistin treatment was 14 days.

Because colistin is primarily excreted by the kidneys, renal toxicity is the most common adverse effect of this drug [19]. Colistin increases the tubular epithelial cell membrane permeability, resulting in an increased influx of cations, anions, and water, leading to cell swelling and lysis [20]. This toxic mechanism may lead to electrolyte deficiency during colistin therapy. Nephrogenesis in the human fetus is not complete until approximately 34–36 weeks of gestation, with > 60% of nephrons being formed in the last trimester of pregnancy, indicating that infants born prematurely continue to form nephrons ex utero. Nephrotoxic medications may

disrupt this process by decreasing the number of nephrons [21]. Conversely, premature kidneys cannot adequately handle free water, electrolytes, small proteins, bicarbonate, and drugs [22–24]. Drug treatment may significantly hamper postnatal kidney development in preterm infants by reducing the formation and number of nephrons [24].

The nephrotoxicity rates due to colistin treatment ranged from 0 to 12% in neonates [6, 9, 12–16]. Alan et al. [9] reviewed 21 preterm infants who were treated with colistin and reported a 19% incidence of nephrotoxicity. Rhone et al. [23] reviewed 107 VLBW infants who received at least one nephrotoxic medication, and the incidence of AKI was found in 27% of the patients. Patients who developed AKI had lower birth weight than those who did not develop AKI in their study. In the present study, AKI was detected in 14% of the VLBW infants (four out of 28) and in 2.6% of the control group (one out of 38); however, no significant difference was observed between the groups.

Table 4 Change in serum electrolytes and liver function tests by colistin treatment

	Before treatment	During treatment (4–7 days of treatment)	<i>p</i> value
VLBW infants			
Mg (mg/dL)	2.04 ± 0.43	1.30 ± 0.33	<0.001
K (mEq/L)	4.77 ± 0.71	3.67 ± 0.96	<0.001
Calcium (mg/dL)	8.8 ± 1.3	8.5 ± 1.3	0.54
AST (IU/L)	33 ± 19	55 ± 69	0.08
ALT (IU/L)	13 ± 6	27 ± 35	0.04
Non-VLBW group			
Mg (mg/dL)	1.96 ± 0.17	1.70 ± 0.28	<0.001
K (mEq/L)	4.63 ± 0.71	4.64 ± 0.72	0.46
Calcium (mg/dL)	9.1 ± 0.6	9.3 ± 0.8	0.27
AST (IU/L)	30 ± 16	39 ± 36	0.11
ALT (IU/L)	17 ± 10	22 ± 18	0.06

Data are presented as mean ± standard deviation or number (%)

ALT alanine aminotransferase, AST aspartate transaminase, K potassium, Mg magnesium, VLBW very low birth weight

Clinical improvement was achieved in two of the five patients after discontinuation of colistin without requiring renal replacement therapy. Similar to the studies conducted by Rhone et al. [23] and Alan et al. [9], we found a higher incidence of AKI in infants with lower birth weight, without a significant difference. Consistent with the report by Alan et al. [9], 53% of our infants required potassium supplementation; however, in the present study, the need for additional magnesium supplementation was higher than that in the Alan study (78 vs 52%, respectively). Lower serum magnesium and potassium levels in VLBW infants during treatment may be related to a decreased number of nephrons in preterm infants. An adult study by Pogue et al. [25] reported that patients who developed nephrotoxicity received significantly higher colistin doses than those who did not (5.48 vs 3.95 mg/kg per day). The cause of the high rates of electrolyte imbalance in our study, particularly in VLBW infants, may be associated with all of our patients receiving standard colistin treatment of 5 mg/kg per day.

Neurotoxicity is another adverse effect of intravenous colistin therapy. Orofacial paresthesias, visual disturbances, vertigo, mental confusion, ataxia, and seizure are neurological side effects of colistin use; however, only apnea and convulsions are recognizable neurological findings in neonates [9, 26]. It is difficult to detect neurological symptoms in preterm infants. As the previous clinical conditions may lead to similar symptoms, it may be difficult to distinguish the neurological side effects of colistin therapy [9]. Most of our patients were premature or receiving sedation/analgesia; therefore, we considered that adverse neurological events,

such as apnea and convulsions, could not be attributed to the colistin treatment in the present study.

There are some limitations to our study. First, the present study was a retrospective study. Second, it was difficult to assess the neurotoxic and nephrotoxic adverse effects because of confounding factors such as administration of sedation to the patients, prematurity, concomitant nephrotoxic medications, sepsis, and shock. Finally, given the concomitant use of other drugs, particularly antibacterials in addition to colistin, adverse effects cannot be attributed solely to colistin.

5 Conclusion

Colistin administration appears to be efficacious in VLBW infants with MDR infection; however, renal function tests and serum electrolytes should be monitored more closely in these infants during treatment. Additional pharmacokinetic and pharmacodynamic studies are needed to determine the optimal dose of colistin in newborn infants with lower birth weight.

Compliance with Ethical Standards

Funding This study did not receive any specific funding.

Conflict of interest Ozkan Ilhan, Meltem Bor, Senem Alkan Ozdemir, Sinem Akbay and Esra Arun Ozer have no conflicts of interest to declare.

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