The Efficacy and Nephrological Side Effects of Treatment with Colistin in Neonates

Yenidoğanlarda Kolistin Tedavisinin Etkililiği ve Nefrolojik Yan Etkileri

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Abstract

Aim: For many years, colistin has not been considered a first-line treatment due to its toxic side effects. However, its use has recently been reevaluated as a last resort in the treatment of neonatal infections caused by multidrug-resistant (MDR) gram-negative bacteria (GNB). Accordingly, in this study we aimed to contribute to the literature by investigating the efficacy and nephrological effects of colistin use in neonates.

Materials and Methods: The retrospective study was conducted in the neonatal intensive care unit of a tertiary university hospital between January 2015 and February 2019 and included 30 patients who received intravenous treatment with colistin for culture-proven hospital-acquired GNB infections. We analyzed the serum sodium, potassium, phosphate, calcium and magnesium levels, urea, creatinine, aspartate aminotransferase and alanine aminotransferase values, and urine outputs measured on the 1st, 3rd, and 10th days of treatment.

Results: All patients were treated with colistin for at least 10 days (mean 16.07±3.22 days) and the treatment dose was 5 mg/kg per day. We observed a statistically significant difference between the 1st- and 10th-day urea, creatinine, calcium, magnesium, and urine output values ($p<0.05$). Similarly, when we compared the measurements recorded on the 1st and 10th days of treatment, we found that the magnesium and calcium levels were significantly decreased (p=0.008 and p=0.038, respectively) while the urea, creatinine, and urine output values were significantly increased (p=0.027, p=0.022, p=0.001, respectively).

Discussion and Conclusion: Colistin is an effective agent in the treatment of MDR-GNB infections in neonates. Neonates should be closely monitored for nephrotoxicity during treatment with colistin. The efficacy and safety of neonatal treatment with colistin should be investigated with further, larger-sample studies.

Keywords: colistin; multidrug resistance; neonates; nephrotoxicity; nosocomial infection

Öz

Amaç: Toksik yan etkileri nedeniyle kolistin, uzun yıllardır ilk seçenek bir tedavi olarak görülmemektedir. Son zamanlarda ise yenidoğanlarda çoklu ilaç dirençli (ÇİD) gram-negatif bakteri (GNB) enfeksiyonlarına karşı son tedavi seçeneği olarak yeniden değerlendirilmektedir. Bu çalışmada da yenidoğanlarda kolistin kullanımının etkililiğini ve nefrolojik yan etkilerini inceleyerek literatüre katkıda bulunmak amaçlanmıştır.

Gereç ve Yöntemler: Retrospektif çalışmamız Ocak 2015—Şubat 2019 döneminde üçüncü basamak bir üniversite hastanesinin yenidoğan yoğun bakım ünitesinde gerçekleştirildi ve kültürle kanıtlanmış hastane kaynaklı GNB enfeksiyonları nedeniyle intravenöz kolistin tedavisi gören 30 hastayı içerdi. Tedavinin 1., 3. ve 10. günlerinde ölçülen serum sodyum, potasyum, fosfor, kalsiyum ve magnezyum düzeyleri, üre, kreatinin, aspartat aminotransferaz, alanin aminotransferaz değerleri ve idrar çıkışları analiz edildi.

Bulgular: Tüm hastalar en az 10 gün (ortalama 16,07±3,22 gün) kolistin tedavisi görmüştü ve tedavi dozu günde 5 mg/kg idi. Birinci ve 10. gün üre, kreatinin, kalsiyum, magnezyum ve idrar çıkış değerleri arasında istatistiksel olarak anlamlı fark olduğu görüldü ($p<0,05$). Benzer biçimde, tedavinin 1. ve 10. gününde kaydedilmiş olan ölçümler karşılaştırıldığında magnezyum ve kalsiyum düzeylerinde anlamlı bir azalma (sırasıyla p=0,008, p=0,038), üre, kreatinin ve idrar çıkış değerlerinde ise anlamlı bir artış (sırasıyla p=0,027, p=0,022, p=0,001) gözlendi.

Tartışma ve Sonuç: Kolistin yenidoğanlarda ÇİD-GNB kaynaklı enfeksiyonların tedavisinde etkili bir ajandır. Yenidoğanlarda kolistin tedavisi sırasında nefrotoksisite yakından izlenmelidir. Yenidoğanlarda kolistin tedavisinin etkililiği ve güvenliliği daha büyük örneklemli, daha ileri çalışmalarla araştırılmalıdır.

Anahtar Sözcükler: çoklu ilaç direnci; hastane enfeksiyonu; kolistin; nefrotoksisite; yenidoğan

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INTRODUCTION

Advances in neonatal intensive care units (NICU) have enabled neonates to survive most life-threatening conditions. However, nosocomial infections still continue to be an important cause of neonatal morbidity and mortality. The risk factors include immunological immaturity, low birth weight, long hospital stays, and exposure to invasive procedures and various drugs (broad-spectrum antibiotics, steroids, etc.) (1).

It is known that the NICU use of broad-spectrum antibiotics leads to infections of multidrug-resistant (MDR) bacteria. Increased incidences of neonatal infections caused by MDR gram-negative bacteria (GNB) have become a major concern as the available treatment options are limited (2,3). *Klebsiella pneumoniae*, *Escherichia coli*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* are the most common MDR-GNB that cause nosocomial infections in neonates (1).

Polymyxin E (colistin) is a cationic polypeptide antibiotic derived from *Bacillus spp*. Since the discovery of polymyxins in 1947, colistin has not been considered a first-line treatment because of its various nephro- and neurotoxic effects. However, polymyxins have recently been reintroduced into the clinical practice as a valuable treatment option for infections caused by GNB that have developed resistance to most of the existing antibiotics (4).

Although the use of colistin for MDR-GNB infections in neonates can be life-saving, the literature contains a limited number of studies on its safety and efficacy in this vulnerable population (5,6). Accordingly, in this study we aimed to investigate and describe the efficacy and renal side effects of treatment with colistin in neonates.

MATERIALS AND METHODS

The retrospective study was conducted in the NICU of the Goztepe Medical Park Hospital of the Bahcesehir University School of Medicine between January 2015 and February 2019 and, based on the medical records reviewed, included a total of 30 patients who received intravenous treatment with colistin for culture-proven hospital-acquired infections caused by MDR-GNB. Clinical data (gestational age, sex, birth weight, history of surgery, intubation and catheterization, length of hospitalization, sample types and infection agents, antibiogram results, and treatment length and response time) were reviewed retrospectively. The serum sodium, potassium, phosphate, calcium and magnesium levels, urea, creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values, platelet (PLT) and white blood cell (WBC) counts, and urine output data recorded on the 1st, 3rd, and 10th days of treatment were also obtained from the hospital records.

Laboratory tests

The AST and ALT levels were determined by using the Abbott Architect ci8200 autoanalyzer (Abbott Park, IL, USA). The PLT and WBC counts were determined by the Sysmex XN-1000 automated blood cell counter (Sysmex Corporation, Kobe, Japan). The blood samples were analyzed by the BacT/ALERT® 3D Microbial Detection System (bioMérieux, France). The gram-negative bacilli colonies isolated from urine and endotracheal aspirate samples after 24 hours of incubation were inoculated into 5% sheep blood agar and antibiotic susceptibility was analyzed by using the VITEK 2 identification and antibiogram system (bioMérieux, Nürtingen, Germany).

Colistin administration and dosage

Intravenous colistin (Colimycin; Kocak Farma, Istanbul, Turkey) was administered for at least 10 days at a dose of 5 mg/kg per day. This colistin formulation contained 150 mg of colistimethate sodium per vial (30,000 IU/mg).

Study ethics

The study protocol was approved by the Bahcesehir University Clinical Research Ethics Committee (protocol no. 2019-10/03).

Statistical analysis

Statistical analyses were performed using the SPSS 22 software (SPSS IBM, Turkey). Conformity with the normal distribution was examined using the Kolmogorov–Smirnov test, Q-Q graphs and histograms. Data were expressed as descriptive statistics (mean, standard deviation, median, frequency, percentage). The Friedman test was used to evaluate the differences

Table 1. Clinical characteristics of the patients (N=30)

Characteristics		Mean±SD or n (%)
Gestational age (weeks)		30.37±4.89
Birth weight (g)		1535.50±946.00
Sex	Female	16 (53.3)
	Male	14 (46.7)
Total parenteral nutrition		17 (56.7)
Use of central venous catheter		8 (26.7)
Duration of catheterization (days) (n=8)		8.75±1.98
Age at the time of hospitalization (days)		123.33±90.18
Age at the time of infection diagnosis (days)		46.60±44.02
Culture-positive sample types	Endotracheal aspirate	18 (60)
	Urine	7 (23.3)
	Blood	5 (16.7)
Microorganisms	*Klebsiella pneumoniae*	17 (56.7)
	Pseudomonas aeruginosa	6 (20)
	Escherichia coli	4 (13.3)
	Acinetobacter baumannii	1 (3.3)
	Acinetobacter lwoffii	1 (3.3)
	Sphingomonas paucimobilis	1 (3.3)
[a] **Antimicrobials prior to colistin**	Aminoglycoside	30 (100)
	Vancomycin	27 (90)
	Carbapenem	30 (100)
	Fluconazole	19 (63)
Initiation of colistin therapy (days)		48.83±44.39
Duration of treatment with colistin		16.07±3.22
[b] **Response time to colistin (days) (n=29)**		5.31±2.41

[a] There were patients treated with more than one antibiotic.

[b] One patient died.

SD: standard deviation

in quantitative time. The Wilcoxon signed-rank test was used to determine the time of difference. The relationship between quantitative data was evaluated by Spearman's rho correlation analysis. $p<0.05$ was considered statistically significant.

RESULTS

Based on the medical records reviewed, we found that 1,104 patients were admitted to the NICU during the study period. Out of these, a total of 30 infants who received intravenous colistin for culture-proven nosocomial infections were included in the study. According to the culture results, the most common (56.7%) cause of nosocomial infection was *Klebsiella pneumonia*, followed by *Pseudomonas aeruginosa* (20%), and *Escherichia coli* (13.3%). Patient clinical characteristics are summarized in Table 1. The differences in laboratory test results recorded during the treatment period are presented in Table 2.

There was a statistically significant difference between the urea and creatinine levels ($p=0.048$ and $p=0.022$, respectively) measured on the 1st, 3rd, and 10th days of treatment. In order to determine the time of the difference in urea levels, bilateral *post hoc* assessments were done; the 10th-day urea levels were significantly higher than those measured on the 1st and 3rd days of treatment ($p=0.027$ and $p=0.032$, respectively). The 10th-day creatinine levels were also higher than the 1st-day measurements ($p=0,022$).

Table 2. Comparison of patient clinical and laboratory test results at different times during treatment with colistin

Results	n	1st day of treatment	3rd day of treatment	10th day of treatment	*p*
		Mean±SD	Mean±SD	Mean±SD	
AST (IU/L)	30	42.27±36.2	38.57±27.1	38.5±27.37	0.875
ALT (IU/L)	30	21.87±16.54	25.43±20.38	21.23±16.64	0.256
Urea (mg/dL)	30	22.90±19.99	29.70±23.21	29.92±23.22	**0.048***
Creatinine (mg/dL)	29	0.47±0.14	0.48±0.16	0.51±0.12	**0.022***
Na (mEq/L)	30	137.7±3.82	137.17±3.43	137.63±3.24	0.939
K (mEq/L)	30	4.29±0.68	4.30±0.91	4.20±0.94	0.500
Ca (mg/dL)	30	9.59±0.95	9.24±1.39	8.89±1.26	**0.047***
Mg (mg/dL)	30	1.81±0.29	1.62±0.36	1.60±0.39	**0.007****
P (mg/dL)	30	4.61±1.27	4.50±1.32	4.69±1.63	0.576
Urine output (mL/kg/h)	29	4.02±0.96	6.19±2.23	5.30±1.50	**0.001****
WBC (x10³/mm³)	30	14.206±17.100	13.177±5.701	11.495±5.697	**0.045***
PLT (x10³/mm³)	30	278.966±161.679	263.833±174.848	288.533±148.975	0.273

The Friedman test, *p<0.05, **p<0.001

ALT: alanine aminotransferase; AST: aspartate aminotransferase; Ca: calcium; K: potassium; Mg: magnesium; Na: sodium; P: phosphate; PLT: platelet; SD: standard deviation; WBC: white blood cell

Moreover, there was a significant difference between the serum calcium and magnesium levels, WBC counts, and urine outputs recorded on the 1st, 3rd, and 10th days of treatment (p=0.047, p=0.007, p=0.045, p=0.001 respectively). Bilateral *post hoc* assessments showed that the 1st-day serum magnesium levels were higher than the 3rd- and 10th-day levels (p=0.008 and p=0.008, respectively). The 1st-day calcium levels were significantly higher than the 10th-day levels (p=0.038). According to bilateral *post hoc* assessments, the 10th-day WBC values were lower than the 1st-day values (p=0.017). The 1st-day urine output values were significantly lower than the 3rd- and 10th-day values (p=0.001 and p=0.001, respectively).

DISCUSSION AND CONCLUSION

In our study, we evaluated 30 patients who were hospitalized in the NICU and treated with colistin for culture-proven nosocomial infections caused by MDR-GNB. There have been a limited number of studies on the efficacy and safety of pediatric treatment with colistin as a last resort against MDR-GNB infections (7–10).

It is known that colistin shows antibacterial activity by changing the permeability of the cell envelope, leading to the leakage of cell substances and cell death (11). However, colistin therapy has adverse effects, which are primarily renal and neurological. In the case of colistin-associated nephrotoxicity, most patients develop acute tubular necrosis within the first week of treatment (3,8). Nephrotoxicity is a concerning adverse effect in the pediatric population as it may present with elevated serum creatinine and blood urea nitrogen levels, cylindruria, hematuria, proteinuria, and acute tubular necrosis. Since colistin is excreted primarily by the kidneys, close monitoring of renal function during treatment with colistin is important. It has been reported that renal toxicity is generally reversible if diagnosed early (12,13), and that the rate of nephrotoxicity during colistin therapy ranges from 8 to 19%, with higher incidences in patients with a history of impaired renal function (3,14–16). In our study, we performed renal function evaluation using estimated glomerular filtration rate based on the Schwartz formula (17), and found that glomerular filtration rate was normal in all patients. However, we found a statistically significant increase in the urea, creatinine, and urine output values during treatment, which is consistent with findings of previous studies.

The neurological adverse effects in adults and children include weakness, oral and perioral paresthesias, ophthalmoplegia, partial deafness, lethargy, ataxia, confusion, seizures, and respiratory muscle paralysis. Colistin-associated neurotoxicity is also reversible and dose-dependent and, according to recent reports, very low, especially in children (8,12,13). Although our subjects were unable to express complaints, according

to the medical records reviewed none had major neurological complications such as seizures.

Currently, the safe dose of intravenous colistin in neonates is not known. Recent studies suggest a dosage of 2.5 to 5 mg/kg per day, which can be divided into 2 to 4 equal doses in children with normal renal functions (3,18). All of our patients had normal renal functions before the treatment and intravenous colistin was administered at a dose of 5 mg/kg per day divided into three equal doses.

It is known that the concomitant use of colistin and certain antibiotics such as carbapenem and rifampicin produces synergistic inhibition (16,19). Also, al-Aloul et al. reported that nephrotoxic effects of aminoglycosides were increased with concomitant use of colistin, although the use of colistin with other, non-nephrotoxic antibiotics did not cause nephrotoxicity (20). Before the culture and antibiotic resistance results were obtained, all patients in our study were empirically administered aminoglycoside and carbapenem, and 90% received vancomycin. Moreover, colistin was combined with meropenem for an enhanced effect, although antibiograms of all isolates showed carbapenem resistance.

In our study, we observed microbiological clearance in 29 (96.7%) of the 30 patients included, while one with MDR *A. baumannii* infection died on the 9th day of treatment. According to recent studies, the rate of favorable clinical results in pediatric treatment with colistin ranges from 72 to 98% (6,9,21,22). Alan et al. reported an efficacy rate of up to 80% in preterm infants with nosocomial infections caused by *A. baumannii*, and stated that most of their subjects who did not respond to colistin treatment were extremely low-birth-weight infants (9). In contrast, in our study the one patient who died was a term infant. Celik et al. reported a mortality rate of 38% in preterm infants with MDR *A. baumannii* infection; however, in their study, only 2 of 21 patients were treated with colistin (23). In a study by Cagan et al., 21% of a total of 65 neonates treated with colistin died during treatment (8). Jajoo et al. reported that 1 of 21 patients treated with colistin had persistence of *A. baumannii* on repeated cultures while the treatment was efficient in 76% (21).

In various studies, neonatal patients were divided into groups according to their birth weight or gestational age. During treatment with colistin, Ilhan et al. found significantly lower levels of serum magnesium and potassium in very-low-birth-weight (<1500 g) infants than in non-low-birth weight neonates. They also stated that serum magnesium levels decreased in both groups while serum potassium levels significantly decreased only in low-birth-weight infants (18). In our study, we did not divide our subjects into groups based on birth weight or gestational age because of the small size of the study sample, and the mean birth weight and gestational age values were 1535.5±946 g and 30.3±4.89 weeks. Alan et al. found an increase in serum creatinine levels during treatment with colistin, and reported that the difference between the values recorded on the first and last days of treatment was statistically significant while in terms of serum electrolytes the only significant difference was observed between the first- and last-day levels of serum magnesium (9). Ipek et al. reported that colistin therapy was associated with reduced magnesium levels and hypokalemia in neonates (7). In our study, both serum magnesium and serum calcium levels significantly decreased during treatment, although no difference was observed in levels of other serum electrolytes.

Finally, our study has several limitations. First, the sample size was small, and similar studies with larger samples are needed to verify our results. Another limitation was the difficulty of determining colistin-related adverse effects due to concomitant medication. Third, we could perform only nephrotoxicity assessments because no adequate neurotoxicity assessment was possible given the ages of the patients.

In conclusion, colistin appears to be an effective agent in the treatment of neonatal infections caused by MDR-GNB. However, serum magnesium, calcium, urea and creatinine levels and urine output values can change significantly during treatment, which requires that neonates under treatment with colistin be closely monitored for nephrotoxicity.

Conflict-of-Interest and Financial Disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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